Study Protocol

P3-C1-019

DARWIN EU® - Suicidality incidence rates in adult male patients and in patients treated with finasteride and dutasteride

19/02/2025

Version 5.0

Contents

Study title	DARWIN EU® - Suicidality incidence rates in adult male patients and in patients treated with finasteride and dutasteride
Protocol version	V5.0
Date	19/02/2025
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Active substance	Therapeutic drug class 5α-reductase inhibitor: finasteride and dutasteride
Medicinal product	n/a
Research question and objectives	What are the incidence rates of suicide-related events in the general adult male population, and adult males with newly diagnosed androgenetic alopecia, and newly diagnosed benign prostatic hyperplasia? The specific objectives are to describe overall incidence rates of suicide-related events in: 1. The general adult male population. 2. Adult male patients with newly diagnosed androgenetic alopecia. 3. Adult male patients with newly diagnosed androgenetic alopecia stratified by treatment (finasteride, dutasteride, topical minoxidil, and no recorded prescription for study treatments). 4. Adult male patients with newly diagnosed benign prostatic hyperplasia (BPH). 5. Adult male patients with newly diagnosed BPH stratified by treatment (finasteride, dutasteride, alpha blockers, tadalafil, tadalafil + finasteride/dutasteride, and no recorded prescription for study treatments). Incidence rates will be stratified by age, history of psychiatric disorder, history of sexual dysfunction, and calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts).
Countries of study	Spain, United Kingdom, Denmark, Germany, The Netherlands, Croatia
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LIST OF ABBREVIATIONS

Acronyms/term	Description
BIFAP	Pharmacoepidemiological Research Database for Public Health System
BPH	Benign Prostatic Hyperplasia
CDM	Common Data Model
CC	Coordinating centre
CIPH	Croatian Institute of Public Health
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
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
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
InGef RDB	InGef Research Database
IP	Inpatient
IPCI	Integrated Primary Care Information
NAJS	The National Public Health Information System Croatia
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalized
SD	Standard Deviation
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
UK	United Kingdom
WHO	World Health Organisation
WONCA	World Organization of Family Doctor

1. TITLE

DARWIN EU® - Suicidality incidence rates in adult male patients and in patients treated with finasteride and dutasteride

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Marzyeh Amini Katia Verhamme	Erasmus MC
Data Scientist(s)	Ross Williams Maarten van Kessel Cesar Barboza Ger Inberg Adam Black	Erasmus MC
Epidemiologist/ Clinical Domain Expert	Marzyeh Amini Katia Verhamme Guido van Leeuwen	Erasmus MC
Data Partner*	**Names**	**Organisation**
BIFAP	Gil Garcia Miguel Jesus, Rebeca Martínez Muñoz Hermenegildo Carlos Martínez-Alcalá García Ana Llorente Garcia Miguel Angel Macia Martinez	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS
CPRD Gold	Antonella Delmestri	University of Oxford
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
InGef RDB	Josephine Jacob Raeleesha Norris Alexander Harms Annika Vivirito	Institut für angewandte Gesundheitsforschung Berlin GmbH
IPCI	Katia Verhamme	Erasmus MC
NAJS	Jakov Vuković Maja Silobrčić-Radić Ivan Pristaš Anamaria Jurčević Pero Ivanko Marko Čavlina Antea Jezidžić	The Croatian National Institute of Public Health
SIDIAP	Talita Duarte-Salles Anna Palomar Agustina Giuliodori Picco	IDIAPJGol

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

3. ABSTRACT

Title

DARWIN EU® – Suicidality incidence rates in adult male patients and in patients treated with finasteride and dutasteride

Rationale and background

Finasteride is a specific inhibitor of 5α-reductase, an enzyme that converts testosterone into dihydrotestosterone. It is approved in Europe for treating benign prostatic hyperplasia (BPH) at 5 mg and androgenetic alopecia at 1 mg and 2.275 mg/dl. Dutasteride, another 5α-reductase inhibitor, is also approved in Europe for moderate-to-severe BPH, either alone or in combination with tamsulosin. In some non-EEA countries, dutasteride is also prescribed for androgenetic alopecia.

Signals of mood changes, including depressed mood, depression, and rarely suicidal ideation, have been reported in patients using finasteride. Depression is listed as a side effect of finasteride, along with anxiety and suicidal thoughts, though their frequency is unknown. These psychiatric effects were not identified during clinical trials but were later explored in post-marketing observational studies. There is insufficient data in the literature regarding the incidence rates of suicide related events in these populations.

The aim of this study is to evaluate the incidence rates of suicide-related events in adult male patients exposed to finasteride or dutasteride medicines for the conditions of androgenetic alopecia and BPH. Having incidence rate data would be helpful to contextualise and to give some insight into the impact of the indication on suicide-related events. Further understanding of the safety of these medicines regarding their potential psychiatric effects can help inform regulatory decisions and the assessment of the benefit/risk profile of these medicines.

Research question and objectives

Research question

What are the overall incidence rates of suicide-related events in the general adult male population, in adult males with newly diagnosed androgenetic alopecia, and/or newly diagnosed benign prostatic hyperplasia, and incidence rates stratified by age group, history of psychiatric disorder, history of sexual dysfunction, calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts)?

Objectives

The specific objectives are to describe overall incidence rates of suicide-related events and stratified by age group, history of psychiatric disorder, history of sexual dysfunction, and calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts) in:

1. The general adult male population.
2. Adult male patients with newly diagnosed androgenetic alopecia.
3. Adult male patients with newly diagnosed androgenetic alopecia initiating treatment for this condition (finasteride, dutasteride, topical minoxidil, and no recorded prescription for study treatments).
4. Adult male patients with newly diagnosed benign prostatic hyperplasia (BPH).
5. Adult male patients with newly diagnosed BPH initiating treatment for this condition (finasteride, dutasteride, alpha blockers, tadalafil, and no recorded prescription for study treatments).

Methods

Study design

Population level cohort study.

Population

The study population will include all adult male patients (≥ 18 years old) present in the data source during the study period (Objective 1).

Within this population 2 sub-cohorts will be nested namely one of adult male patients newly diagnosed with androgenetic alopecia and one consisting of adult male patients newly diagnosed with BPH (Objectives 2 and 4).

Within these cohorts of adult males newly diagnosed with androgenetic alopecia and BPH, we will nest cohorts of individuals initiating treatments of interest for the first time in the study period (Objectives 3 and 5).

Study period

Study period will start from 2010 until the end of available data. In the InGef RDB and NAJS data sources, data will be available from 2014 and 2017, respectively.

Variables

Exposures

Conditions of interest (androgenetic alopecia and BPH) and treatments for these conditions (i.e., finasteride, dutasteride, topical minoxidil, alpha blockers, tadalafil, and tadalafil + finasteride/dutasteride).

Outcome

Outcome of interest will be a composite suicidality outcome which will include the first recorded occurrence of any of the following events: completed suicide, attempted suicide, suicide ideation, and intentional self-harm.

Relevant covariates

Age groups, history of psychiatric disorder, history of sexual dysfunction, and calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts).

Data source

1. Pharmaco-epidemiological Research Database for Public Health Systems (BIFAP), Spain
2. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom
3. Danish Data Health Registries (DK-DHR), Denmark
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), Netherlands
6. Croatian National Public Health Information System (NAJS), Croatia
7. The Information System for Research on Primary Care (SIDIAP), Spain

Sample size

No sample size has been calculated as this is an exploratory study which will not test a specific hypothesis. To estimate the incidence rates of suicide-related events in adult male patients diagnosed with androgenetic alopecia and BPH, we will use already collected available data. Thus, the sample size will be driven by the availability of patients with conditions of interest, exposures and outcomes within each database.

Statistical analysis

Incidence rates of suicide-related events per 1,000 person-years (PYs) will be estimated in the general population of adult males and in adult male patients newly diagnosed with androgenetic alopecia and/or BPH. Within these populations, incidence rates of suicide-related events per 1,000 PYs will also be calculated among patients exposed to the drugs of interest (i.e., treatments of androgenetic alopecia and BPH). Overall incidence rates will be reported as well as stratified by age categories, history of psychiatric disorders, history of sexual dysfunction, and calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts). Incidence rates will be given together with 95% Poisson confidence intervals. The statistical analyses will be performed based on OMOP-CDM mapped data using "*IncidencePrevalence*" R package. 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
Draft Study Protocol	5 November 2024
Final Study Protocol	22 November 2024
Creation of Analytical code	25 November 2024
Execution of Analytical Code on the data	2 December 2024
Draft Study Report	13 December 2024
Final Study Report	31 January 2025

6. RATIONALE AND BACKGROUND

Finasteride is a specific inhibitor of type-II 5α-reductase, an intracellular enzyme that metabolizes the androgen testosterone into dihydrotestosterone. Finasteride has been authorised in Europe since 1992 for the treatment of BPH (5mg) and since 1998 for the treatment of androgenetic alopecia (1 mg, 2.275 mg/dL).(1-3) Another 5α-reductase inhibitor indicated for the treatment of moderate-to-severe symptoms of BPH is dutasteride. It has been authorised in Europe since 2002 as monotherapy or in fixed dose combination (0.5mg) with tamsulosin (0.4 mg).(4) In some countries outside the EEA, notably South Korea and Japan, dutasteride is also authorised for androgenetic alopecia.(5, 6)

Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported as side effect in patients treated with finasteride.(1, 7) Additionally, anxiety and suicidal thoughts are listed among the side effects, although their frequency is unknown.(8-11) Concerns persist about the potential continuation of psychiatric events and risks of suicide or self-injury even after discontinuing finasteride, particularly in young patients, which are being closely monitored.(12, 13) The psychiatric and suicidal adverse effects of finasteride were not found during clinical trials, but these side effects were later investigated in post-marketing observational studies.(14, 15) However, the evidence is currently scarce, and it is unclear if these psychiatric side effects could be due to the medicine itself. It is also unclear if these effects might be mediated by the potential impact on sexual side effects (sexual dysfunction) of these medicines.(14)

The aim of this study is to evaluate the incidence rates of suicide-related events in adult male patients exposed to finasteride or dutasteride for the treatment of androgenetic alopecia and BPH. Further understanding of the safety of these medicines regarding their potential psychiatric effects can help inform regulatory decisions and the assessment of the benefit/risk profile of these medicines.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the overall incidence rates of suicide-related events in the general adult male population, as well as in adult male patients newly diagnosed with androgenetic alopecia and/or benign prostatic hyperplasia (BPH), stratified by age group, history of psychiatric disorder, history of sexual dysfunction, and calendar year (for the general adult male population) and /follow-up year (for indication and treatment cohorts)?

Objectives

The proposed objectives to be achieved in the study are described in **Table 1**.

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective(s):	To describe incidence rates of suicide-related events, overall and stratified by age groups, history of psychiatric disorder, history of sexual dysfunction and calendar year (for the general adult male population) and /follow-up year (for indication and treatment cohorts in: 1. The general adult male population. 2. Adult male patients newly diagnosed with androgenetic alopecia. 3. Adult male patients newly diagnosed with androgenetic alopecia initiating treatment for this condition (finasteride, dutasteride, topical minoxidil, and no recorded prescription for study treatments). 4. Adult male patients newly diagnosed with benign prostatic hyperplasia (BPH). 5. Adult male patients newly diagnosed with BPH initiating treatments for this condition (finasteride, dutasteride, alpha blockers, tadalafil, tadalafil + finasteride/dutasteride, and no recorded prescription for study treatments).
Hypothesis:	n/a
Population *(mention key inclusion-exclusion criteria):*	The study population will include all adult male population (≥ 18 years) present in the data source during the study period. The study period will start from 2010 until the end of available data, except in InGef RDB and NAJS data sources in which data are available from 2014 and 2017, respectively. Within this population two sub-cohorts will be nested, namely one on adult male patients newly diagnosed with androgenetic alopecia and one consisting of adult male patients newly diagnosed with BPH. Within these cohorts of adult males newly diagnosed with androgenetic alopecia and BPH, we will nest cohorts of individuals initiating treatments of interest for the first time at any time following diagnosis.

Exposures:	Conditions of interest (androgenetic alopecia and BPH) and treatments for these conditions (i.e., finasteride, dutasteride, topical minoxidil, alpha blockers, tadalafil, and tadalafil + finasteride/dutasteride).
Comparator:	n/a
Outcome:	The outcome of interest is a composite suicidality outcome which will include the first recorded occurrence of the following events: completed suicide, attempted suicide, suicide ideation, and intentional self-harm.
Time *(when follow up begins and ends):*	Objective 1: General adult male population Follow-up will start on the first date, within the study period, when an individual becomes eligible to enter the study and will continue until the earliest of the following: first date of a study outcome of interest, loss to follow-up, death, end of observation period (the most recent data available) in the database. Objectives 2 and 4: Adult males with incident androgenetic alopecia or incident BPH Follow-up will start from the date of incident androgenetic alopecia or incident BPH diagnosis during the study period and will continue until the earliest of the following: first date of a study outcome of interest, loss to follow-up, death, end of observation period (the most recent data available) in the database. Objective 3 and 5: Adult males with incident androgenetic alopecia or BPH who initiate treatments Follow-up will start on the date of the first treatment of interest initiation following a newly diagnosed androgenetic alopecia or BPH and will continue up until the first of the following: first date of a study outcome event, the date of treatment discontinuation plus six months, switching to another treatment cohort, loss to follow-up, death, end of observation period (the most recent data available) in the database.
Setting:	Outpatient setting using data from the following 7 data sources: BIFAP (Spain), CPRD GOLD (UK), DK-DHR (Denmark), InGef RDB (Germany), IPCI (The Netherlands), NAJS (Croatia), SIDIAP (Spain)
Main measure of effect:	Incidence rates of suicide-related events (with 95% confidence intervals)

8. RESEARCH METHODS

8.1 Study type and study design

This will be a population level disease epidemiology study classified as "*off-the-shelf*" and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (**Table 2**).(16) Overall incidence rates of suicide-related events in patients diagnosed with androgenetic alopecia and with BPH will be described as

well as overall incidence rates of suicide-related events in patients who initiated treatments for androgenetic alopecia and BPH (finasteride, dutasteride, etc.). These incidence rates will be also presented stratified by age group, history of psychiatric disorder, history of sexual dysfunction and calendar year (for the general adult male population) and follow-up year (for indication and treatment cohorts).

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population-Level Descriptive Epidemiology	Population-Level Cohort	Off the shelf

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 7 primary/secondary care databases in the DARWIN EU® network of data partners from 6 European countries. With regards to conditions of interest, exposures and outcome, only 4 out of the 7 selected data sources have been *a priori* mapped to the OMOP CDM. Three data sources (i.e., 1, 3, and 4 in the list below) will be mapped during the conduct of this study (December 2024).

Data sources

1. Pharmacoepidemiological Research Database for Public Health Systems (BIFAP), Spain
2. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom
3. Danish Data Health Registries (DK-DHR), Denmark
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), Netherlands
6. Croatian National Public Health Information System (NAJS), Croatia
7. The Information System for Research on Primary Care (SIDIAP), Spain

Data Selection

These databases fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for population level descriptive epidemiology while covering different regions of Europe. Detailed information on the selected data sources is described in **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 utilised the Achilles tool,(17) which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, 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), 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 (see Section D1.3.5.2 on Complete Data Quality Assurance Package) on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of databases was based on the availability of data on the selected conditions (androgenetic alopecia and BHP), the treatments and the outcome of interest to perform the described analyses. In addition, the databases 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 databases have information on use of treatments and indications of interest. 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 database, as this can vary across different domains. To facilitate this, the C*DMOnboarding* (and *Achilles*) packages (17) contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows to get insights when data collection started, when new sources of data were added and until when data was included. In addition, at 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 (18) and DrugExposureDiagnostics (19), 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.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active persons*	Feasibility count of finasteride and dutasteride**	Feasibility count of androgenetic alopecia and BPH**	Feasibility count of suicide related events**	From the start date of data registration to the data lock date of the most recent update
Spain	BIFAP	Adequate number of patients exposed to drugs of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of BIFAP contributes to geographical diversity of data sources included.	Primary care, inpatient hospital care	EHRs, claims, registries	16.9m	8,700 and 68,800	22,400 and 75,900	41,900	01/09/1998 - 02/05/2024
United Kingdom	CPRD-GOLD	Adequate number of patients exposed to drug of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of CPRD contributes to geographical diversity of data sources included.	Primary care	EHR	2.92m	143,200 and 32,600	2,300 and 140,700	61,400	01/10/1987 - 01/01/2024

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active persons*	Feasibility count of finasteride and dutasteride**	Feasibility count of androgenetic alopecia and BPH**	Feasibility count of suicide related events**	From the start date of data registration to the data lock date of the most recent update
Denmark	DK-DHR	Adequate number of patients exposed to drugs of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of DK-DHR contributes to geographical diversity of data sources included.	Inpatient hospital care and secondary outpatient care	EHRs, registries, others	5.96m	71,100 and 19,900	1,500 and 100	9,900	01/01/1995 - 21/05/2024
Germany	InGef RDB	Adequate number of patients exposed to drug of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of InGef RDB contributes to geographical diversity of data sources included.	Primary care, hospital inpatient care and secondary outpatient care	Claims	7.6m	49,100 and 35,700	1,600 and 193,100	10,400	01/01/2014 - 01/04/2024
The Netherlands	IPCI	Adequate number of patients exposed to drug of interest, medical conditions, and outcomes	Primary Care	EHR	1.25m	13,700 and 15300	14,400 and 30,000	8,200	01/01/2006 - 30/04/2024

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active persons*	Feasibility count of finasteride and dutasteride**	Feasibility count of androgenetic alopecia and BPH**	Feasibility count of suicide related events**	From the start date of data registration to the data lock date of the most recent update
		within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of IPCI contributes to geographical diversity of data sources included.							
Croatia	NAJS	Adequate number of patients exposed to drug of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data availability over the study period and continuous follow-up of the patients included. Use of NAJS contributes to geographical diversity of data sources included.	Primary care, outpatient specialist care, and inpatient care	Registries	4.22m	41,400 and 49,000	5,800 and 431,300	8,600	01/08/1993 - 17/11/2023
Spain	SIDIAP	Adequate number of patients exposed to drug of interest, medical conditions, and outcomes within the patient records (as documented in the feasibility assessment), adequate data	Primary care	EHR	5.95m	71,800 and 89,000	12,600 and 43,100	26,500	01/01/2006 - 30/06/2023

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active persons*	Feasibility count of finasteride and dutasteride**	Feasibility count of androgenetic alopecia and BPH**	Feasibility count of suicide related events**	From the start date of data registration to the data lock date of the most recent update
		availability over the study period and continuous follow-up of the patients included. Use of SIDIAP contributes to geographical diversity of data sources included.							

* Active persons are defined as the maximum number of persons in an observation period of each data source, in the last 6 months.

**Based on person counts from approved feasibility assessment.

BPH= Benign Prostatic Hyperplasia

Pharmacoepidemiological Research Database for Public Health Systems (BIFAP), Spain

BIFAP (http://www.bifap.org/?lang=en) is a longitudinal population-based data source of medical patient records of the Spanish National Health Service. It includes data from 9 of Spain's 17 autonomous regions. Population currently included represents 36% of the total Spanish population. The Spanish National Health Service provides universal access to health services through the Regional Healthcare Services. Primary care physicians, both general practitioners (GP) and paediatricians, act as gatekeepers of the system and exchange information with other levels of care to ensure the continuity of care. Most of the population (98.9%) is registered with a primary care physician and most drug prescriptions are written at the primary care level. BIFAP includes a collection of databases linked at individual patient level. The main one is the Primary care Database given the central role of primary care physicians in the Spanish National Health Service. Linked, there are additional important structural databases like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge. Additional databases are also linked for a subset of patients (hospital pharmacy, cause of death registry). BIFAP program is a non-profit program financed by the Spanish Agency of Medicines and Medical Devices (AEMPS), a government agency belonging to the Ministry of Health in collaboration with the regional health authorities. The main use of BIFAP is for research purposes to evaluate the adverse and beneficial effects of drugs and drug utilisation patterns in the general population under real conditions of use.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

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.(20) 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. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.(20) 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.(21-23)

Danish Data Health Registries (DK-DHR), 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 cradle to grave, 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. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. 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, and Coronavirus disease 2019 test and vaccination Registries.

InGef Research Database (InGef RDB), Germany

The InGef RDB comprises anonymized longitudinal claims data of about 10 million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef RDB are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef RDB includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensing of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef RDB: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef RDB is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database.

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.(24) IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented and IPCI has proved valuable for epidemiological studies.(25-29) In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, proportion of patients with blood pressure measurement, etc.(24) Based on this information, two quality scores have been created. Practices with low scores have been excluded.

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 (CIPH). 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 2017.

Information System for Research in Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.(30) It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented and SIDIAP has proved valuable for epidemiological studies.(31-39) In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values) and consistency using visualization tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

8.3 Study period

Even though finasteride received marketing approval in 1992, and dutasteride in 2002, the start of the study period will be set to 2010 (i.e., 01 January 2010) when most of the data sources have enough data of treatments of interest until the end of available data. It should be noted that in the InGef RDB and NAJS data sources, the availability of data starts from 01 January 2014 and 01 January 2017, respectively.

8.4 Follow-up

- The cohort of general adult male population (Objective 1): Follow-up will start on the first date, within the study period, when an individual becomes eligible to enter the study (i.e., index date as defined in **Table 4**), and will continue until the earliest of the following: first date of the study outcome of interest, loss to follow-up, death, end of observation period (the most recent data available) in the database.

- For the cohorts of adult male patients with incident androgenetic alopecia or BPH (Objectives 2 and 4): Follow-up will start from the index date (i.e., first diagnosis ever of androgenetic alopecia or BPH diagnosis recorded during the study period, see Table 4) and will continue until the earliest of the following: first date of the study outcome of interest, loss to follow-up, death, end of observation period (the most recent data available) in the database.
- For the cohorts of adult male patients with incident androgenetic alopecia and/or BPH who initiated treatments for these conditions (Objective 3 and 5): Follow-up will start from index date (i.e., date of initiation of first treatment of interest) any time following incident androgenetic alopecia and BPH diagnosis during the study period (see **Table 4**), and will continue up until the earliest of the following: first date of the study outcome of interest event, the date of treatment discontinuation plus six months, switching to another treatment cohort, loss to follow-up, death, end of observation period (the most recent data available) in the database.
- For the cohorts of adult male patients with androgenetic alopecia or BPH who had no recorded prescription for study treatments related to these conditions (Objective 3 and 5): Follow-up started from index date (i.e., first diagnosis ever of androgenetic alopecia or BPH diagnosis recorded during the study period)**Table 4**, and continued up until the earliest of the following: first date of the study outcome of interest event, the first date of treatment with study treatments, loss to follow-up, death, end of observation period (the most recent data available) in the data source.

Operational definition of the index dates for each of the cohorts mentioned above and other primary time anchors are described in **Table 4**.

Table 4. Operational definition of time 0 (index date).

Study population name(s)	Time Anchor Description (time 0 or index date)	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
General adult male population older than 18 years old (objective 1)	First date, during the study period, on which individuals are minimum 18 years of age and have sufficient prior data availability (minimum 365 days)	Single	n/a	n/a	OP	n/a	n/a	n/a	n/a	n/a
Adult males with incident androgenetic alopecia (objective 2)	First diagnosis androgenetic alopecia (incident diagnosis), with sufficient prior data availability (minimum 365 days)	Single	Incident	Any time prior to study entry date	OP	Clinical finding	n/a	Prior androgenetic alopecia diagnosis	n/a	n/a
Adult males with incident BPH (objective 4)	First date of BPH diagnosis (incident diagnosis), with sufficient prior data availability (minimum 365 days)	Single	Incident	Any time prior to study entry date	OP	Clinical finding	n/a	Prior BPH diagnosis	n/a	n/a
Adult males with incident androgenetic alopecia (objective 3) initiating treatment with any of the medicines of interest	Date of first treatment with topical minoxidil, finasteride or dutasteride (see Section 8.6.1) any time following the diagnosis of androgenetic alopecia during study period,	Single	Incident	Any time prior to study entry date	OP	Treatment	n/a	Prior selected treatments of interest,	n/a	n/a

Study population name(s)	Time Anchor Description (time 0 or index date)	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
	with sufficient prior data availability (minimum 365 days)									
Adult males with incident BPH (objective 5) initiating treatment with any of the medicines of interest	Date of first treatment with alpha blocker, finasteride, dutasteride or tadalafil (see Section 8.6.1) any time following the diagnosis of BPH during study period, with sufficient prior data availability (minimum 365 days)	Single	Incident	Any time prior to study entry date	OP	Treatment	n/a	Prior selected treatments of interest,	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 another primary anchor) criterion

BPH= Benign Prostatic Hyperplasia

8.5 Inclusion and exclusion criteria

The study population will be defined as follows for each cohort:

For the cohort of general adult male population (Objective 1):

Inclusion criteria:

- All male patients aged ≥18 years observed in one of the participating data sources during the study period.
- Minimum 365 days of available history before index date.

Exclusion criteria:

- Patients with a recorded history of suicide-related or self-harm-related events (as defined in Outcome section, composite suicidality outcome) prior to index-date.

For the cohorts of adult male patients with incident androgenetic alopecia or BPH (Objectives 2 and 4):

Within the general adult male population, two sub-cohorts will be nested, one for each condition of interest (i.e., androgenetic alopecia and BPH).

Inclusion criteria:

- Same as described above for the general adult male population.
- Patients newly diagnosed (first diagnosis recorded in the database) with:
    - Androgenetic alopecia, OR
    - BPH.

Exclusion criteria:

- Same as described above for the general adult male population.
- A previous diagnosis of androgenetic alopecia OR BPH before index date.

For the cohorts of adult male patients with androgenetic alopecia or BPH who initiated treatments for these conditions (Objective 3 and 5):
Within the cohorts of adult males newly diagnosed with androgenetic alopecia and BPH, we will nest cohorts of patients initiating treatment for these conditions any time following diagnosis.

Inclusion criteria:

- Same as described above for the male patients with incident androgenetic alopecia or BPH.
- Patients initiating treatments of interest (see Section 8.6.1) for the first time following the first diagnosis of androgenetic alopecia or BPH.

Exclusion criteria:

- Same as described above for the general adult male population.
- For the treatment cohorts of patients initiating finasteride or dutasteride for androgenetic alopecia, previous treatment with any of the study treatments (see Section 8.6.1) except topical minoxidil before index date.
- For the treatment cohort of patients initiating topical minoxidil, previous treatment with any of the study treatments before index date.
- For the treatment cohorts of patients initiating finasteride, dutasteride or tadalafil for BPH, previous treatment with any study treatments except alpha-blockers before index date.
- For the treatment cohorts of patients initiating alpha-blockers for BPH, previous treatment with any study treatments before index date.

Operational definition of the inclusion and exclusion criteria for each of the cohorts mentioned above are described in **Table 5** and **Table 6**, respectively.

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 study period	All adult male individuals present in the study period	After study start date	n/a	OP, OT	n/a	n/a	All adult male individuals within selected databases	n/a	n/a
Prior database history of one year	Study participants will be required to have a year of prior history observed before contributing observation time	Before index date/study start date	[-365, -1]	OP, OT	n/a	n/a	All adult male individuals within selected databases	n/a	n/a
Adult	Aged ≥18 years at index date	After study start date	On index date	OP	n/a	n/a	All cohorts	n/a	n/a
Sex	Male	After study start date	On index date	OP	n/a	n/a	All cohorts	n/a	n/a
Androgenetic alopecia	Diagnosis records of androgenetic alopecia	After study start date	On index date	OP, OT	SNOMED	n/a	Androgenetic alopecia cohort	n/a	n/a
BPH	Diagnosis records of androgenetic alopecia	After study start date	On index date	OP, OT	SNOMED	n/a	BPH cohort	n/a	n/a
Initiating treatments of interest for androgenetic alopecia	Treatment with finasteride, dutasteride, topical minoxidil after androgenetic alopecia diagnosis.	After condition index date	On index date	OP, OT	RxNorm	n/a	Androgenetic alopecia treatment cohorts	n/a	n/a

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
Initiating treatments of interest for BPH	Treatment with finasteride, dutasteride, alpha blocker, tadalafil, after BPH diagnosis.	After condition index date	On index date	OP, OT	RxNorm	n/a	BPH treatment cohorts	n/a	n/a

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

[2] The type(s) of clinical codes that are used to define the inclusion criteria.

BPH= Benign Prostatic Hyperplasia

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting "before" means that all possible study entry dates are identified, and then one or more is chosen. 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. If the patient does not meet the criterion, then the patient drops out.

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Observation	Less than 365 days of observation prior to the index date	After	[-365,0]	OP, IP, and OT	n/a	N/A	All cohorts	n/a	n/a
Previous history of composite suicidality outcomes	Recorded history of suicide-related or self-harm-related events (as defined in outcome section, composite suicidality outcome) prior to the index-date	Before	any time prior to index date	IP, OP, and OT	RxNorm	n/a	All cohorts	n/a	n/a

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Previous diagnosis of androgenetic alopecia before index date	Diagnosis records of androgenetic alopecia prior to the index date.	Before	any time prior to index date	OP, OT	SNOMED	n/a	Androgenetic alopecia cohort	n/a	n/a
Previous diagnosis of BPH before index date	Diagnosis records of BPH prior to the index date	Before	any time prior to index date	OP, OT	SNOMED	n/a	BPH cohort	n/a	n/a
Previous treatment with any of the study treatments except minoxidil before index date	Treatment with index drug, finasteride or dutasteride prior to the index date for androgenetic alopecia	Before	any time prior to index date	OP, OT	RxNorm	n/a	Treatment cohorts initiating finasteride or dutasteride for androgenetic alopecia	n/a	n/a
Previous treatment with any of the study treatments before index date	Treatment with index drug, prior to the index date for androgenetic alopecia	Before	any time prior to index date	OP, OT	RxNorm	n/a	Treatment cohorts initiating minoxidil for androgenetic alopecia	n/a	n/a

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Previous treatments of interest for BPH except alpha-blockers prior index date	Treatment with index drug, finasteride, dutasteride, or tadalafil prior to index date for BPH	Before	any time prior to index date	OP, OT	RxNorm	n/a	Treatment cohorts initiating finasteride, dutasteride, or tadalafil for BPH	n/a	n/a
Previous treatments of interest for BPH prior index date	Treatment cohorts with index drug, alpha-blockers prior to index date for BPH	Before	any time prior to index date	OP, OT	RxNorm	n/a	Treatment cohorts of patients initiating alpha-blockers for BPH	n/a	n/a

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

[2] The type(s) of clinical codes that are used to define the inclusion criteria.

8.6 Variables

8.6.1 Exposure/s

- Cohorts of conditions of interest will be defined as follows in **Table 7**:

Table 7. Operational definitions of exposure to conditions of interest.

Condition of interest	Definition	Follow-up (censoring)
Androgenetic alopecia	Individuals with a first diagnosis of androgenetic alopecia	Follow-up will start from the date of incident androgenetic alopecia diagnosis during the study period (after a minimum of 365 days of database history). Follow up ends at the earliest date of 1) outcome of interest occurrence, 2) loss to follow-up, 3) death, 4) end of observation period (the most recent data available) in the database.
Benign prostatic hyperplasia (BPH)	Individuals with a first diagnosis of BPH	Follow-up will start from the date of incident BPH diagnosis during the study period (after a minimum of 365 days of database history). Follow up ends at the earliest date of 1) outcome of interest occurrence, 2) loss to follow-up, 3) death, 4) end of observation period (the most recent data available) in the database.

- Cohorts of treatments of interest will be defined as follows in **Table 8**:

Table 8. Operational definitions of exposure to treatment of interest.

Treatment cohorts	Definition	Follow-up (censoring)
Androgenetic alopecia indication		
Finasteride	Individuals who initiate finasteride, after the first diagnosis of androgenetic alopecia. Treatments other than dutasteride (mainly topical, including minoxidil) are allowed before or during follow-up.	Follow-up starts at first finasteride prescription any time following the first diagnosis of androgenetic alopecia. Follow-up ends at the date of treatment discontinuation plus six months or when the participant switches to (i.e., initiates) dutasteride, if this comes before the first outcome event or any other previously described censoring event.
Dutasteride	Individuals who initiate dutasteride, after the first diagnosis of androgenetic alopecia. Treatments other than finasteride (mainly topical, including minoxidil) are allowed before or during follow-up.	Follow-up starts at first dutasteride prescription any time following the first diagnosis of androgenetic alopecia. Follow-up ends at the date of treatment discontinuation plus six months or when the participant switches to (i.e., initiates) finasteride, if this comes before the first

Treatment cohorts	Definition	Follow-up (censoring)
		outcome event or any other previously described censoring event.
Topical minoxidil	Individuals who initiate topical minoxidil, after the first diagnosis of androgenetic alopecia. Treatments other than finasteride or dutasteride are allowed before or during follow-up.	Follow-up starts at first topical minoxidil prescription any time following the first diagnosis of androgenetic alopecia. Follow-up ends at the date of treatment discontinuation plus six months or when the participant initiates finasteride or dutasteride, if this comes before the first outcome event or any other previously described censoring event.
No recorded prescription for study treatments	Individuals who do not initiate any of the above-mentioned treatments for androgenetic alopecia. Treatments other than those mentioned above are allowed before or during follow-up.	Follow-up starts at first androgenetic alopecia diagnosis. Follow-up ended at the earliest date of 1) outcome of interest occurrence, 2) loss to follow-up, 3) death, 4) end of observation period (the most recent data available) in the data source, 5) initiation of any study treatment for androgenetic alopecia.
BPH indication		
Finasteride	Individuals who initiate finasteride, either alone or in combination with alpha blockers, after first BPH diagnosis. Treatments other than dutasteride and tadalafil are also allowed before or during follow-up.	Follow-up starts at first finasteride prescription any time following first BPH diagnosis. Follow-up ends at the date of treatment discontinuation plus six months or the participant initiates dutasteride or tadalafil, if this comes before the first outcome event or any other previously described censoring event.
Dutasteride	Individuals who initiate dutasteride, either alone or in combination with alpha blockers, after first BPH diagnosis. Treatments other than finasteride and tadalafil are also allowed before or during follow-up.	Follow-up starts at first dutasteride prescription any time following first BPH diagnosis. Follow-up ends at the date of treatment discontinuation plus six months or the participant initiates finasteride or tadalafil, if this comes before the first outcome event or any other previously described censoring event.
Alpha blockers	Individuals who initiate any alpha blocker after first BPH diagnosis. Treatments other than finasteride, dutasteride and tadalafil are also allowed before or during follow-up.	Follow-up starts at first alpha blocker prescription within any time following first BPH diagnosis. Participants are allowed to switch between alpha blockers. Follow-up ends at the date of treatment discontinuation plus six months or the participant initiates dutasteride, finasteride or tadalafil, if this comes before the first

Treatment cohorts	Definition	Follow-up (censoring)
		outcome event or any other previously described censoring event.
Tadalafil	Individuals who initiate tadalafil, either alone or in combination with alpha blockers, after first BPH diagnosis. Treatments other than finasteride and dutasteride are also allowed before or during follow-up.	Follow-up starts at first tadalafil prescription any time following first BPH diagnosis. Follow-up ends at the date of treatment discontinuation plus six months or the participant initiates finasteride or dutasteride, if this comes before the first outcome event or any other previously described censoring event.
Tadalafil + Finasteride/Dutasteride	Individuals who initiate tadalafil in combination with finasteride or dutasteride and possibly in combination with alpha blockers, after first BPH diagnosis. Other treatments (anti-cholinergic, beta 3 agonists, herbals) are also allowed before or during follow-up.	Follow-up starts at first tadalafil + finasteride/dutasteride prescription any time following the first BPH diagnosis. Follow-up ends at the date of treatment discontinuation plus six months or any other previously described censoring event. No switch is a censoring event.
No recorded prescription for study treatments	Individuals who do not initiate any of the above mentioned BPH treatments. Treatments other than those mentioned above are allowed before or during follow-up (anti-inflammatory, anti-cholinergic, beta-3 agonists, herbal etc.)	Follow-up starts at first BPH diagnosis. Follow-up ended at the earliest date of 1) outcome of interest occurrence, 2) loss to follow-up, 3) death, 4) end of observation period (the most recent data available) in the data source, 5) initiation of any study treatment for BPH.

A preliminary list of conditions and exposure concepts can be seen in **Appendix I, Table S 1** and **Table S 2**.

8.6.2 Outcome/s

The outcome of interest is a composite suicidality outcome which will include the first recorded occurrence of any following events: completed suicide, attempted suicide, suicide ideation, and intentional self-harm.

All preliminary lists of codes for identifying the outcomes of interest are available in **Appendix I, Table S 3.**

These will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating databases.

Furthermore, we will describe the counts of the constituent parts which make up the composite suicidality outcome, i.e., the number of outcomes which are attributed to suicide, suicide attempt, suicide ideation, and self-harm.

The operational definition of the outcome is presented in the **Table 9**.

Table 9. Operational definition of outcomes.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Composite suicidality outcome	First condition/observation record of any of the following events of completed suicide, attempted suicide, suicide ideation, and intentional self-harm	Yes	Binary	[-inf , -1]*	IP, OP, and OT	SNOMED	n/a	All cohorts	n/a	n/a

* Infinite wash out will be applied which means we will include only incident cases and not allowing outcome event any time before index date

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

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

- Age at index date namely:
  - 18-30 years
  - 31-40 years
  - 41-50 years
  - 51-60 years
  - 61-70 years
  - 71+years

- History of psychiatric disorders, which will include any of the following conditions:
  - Depression
  - Anxiety
  - Bipolar disorder
  - Post-traumatic stress disorder (PTSD)
  - Eating disorders
  - Psychotic disorders

- History of sexual dysfunction, which will include any of the following conditions:
  - Sexual pain disorder
  - Sexual arousal disorder
  - Sexual desire disorder
  - Psychosexual disorder

- Calendar/follow-up year: calendar year for the general population and follow-up year for indication and treatment cohorts.

List of codes for identifying the psychiatric disorders and sextual dysfunction are described in **Appendix I, Table S 1.**

The operational definitions of the covariates are described in the **Table 10**.

Table 10. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Demographics	Age at index date	Numeric continuous	At index date	IP, OP, and OT	n/a	n/a	All cohorts	n/a	n/a
Psychiatric disorders of interest	Diagnosis records prior index date	Binary	All history before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a
Sexual dysfunction	Diagnosis records prior index date	Binary	All history before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a
Calendar/follow-up year	Calendar year for the general adult male population and follow-up year for indication and treatment cohorts	Numeric	At index date and during follow-up	IP, OP, and OT	n/a	n/a	All cohorts	n/a	n/a

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

BPH= Benign Prostatic Hyperplasia

8.7 Study size

No sample size has been calculated as this is an exploratory study which will not test a specific hypothesis. In addition, to estimate the incidence rates of suicide-related events in adult male patients diagnosed with androgenetic alopecia and BPH, we will use already collected available data. Thus, the sample size will be driven by the availability of patients with conditions of interest, exposures and outcomes within each database. Based on a preliminary feasibility assessment, the expected number of persons counts for androgenetic alopecia in the databases included in this study range from 1,500 (DK-DHR) to 14,400 (IPCI) and for BPH from 100 (DK-DHR) to 431,300 (NAJS). These numbers are based on the overall number of conditions registries in each database with no filter by study period or inclusion and exclusion criteria.

8.8 Analysis

The analysis will include the calculation of incidence rates, as described in section 8.8.5. The type of analysis by study type is presented in **Table 11**.

Table 11. Description of study type and type of analysis.

Study type	Study classification	Type of analysis
Population-level descriptive epidemiology	Off-the-shelf	- Incidence rates of the condition of interest

8.8.3 Federated network analyses

All analyses will be conducted separately for each database, 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 11 Quality Control), 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). All results will be locked and timestamped for reproducibility and transparency. 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.

8.8.4 Patient privacy protection

All analyses will be conducted separately for each database, 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 database's privacy protection regulations.

8.8.5 Statistical model specification and assumptions of the analytical approach considered

R-packages

The incidence rates will be calculated based on OMOP-CDM mapped data using the "*IncidencePrevalence*" R package, developed by DARWIN EU®.(40)

- Descriptive analysis:

Distribution (number and %, median and IQR) of patient characteristics for each cohort of interest will be described by data sources. This includes the general population, the androgenetic alopecia cohort, the treated androgenetic alopecia cohort, the BPH cohort, and the treated BPH cohort.

Furthermore, we will describe the counts of the constituent parts which make up the composite suicidality outcome, i.e., the number of outcomes which are attributed to suicide, suicide attempt, suicide ideation, and self-harm.

- Main analysis:

Overall incidence rates of the outcomes of interest will be calculated as the number of newly diagnosed individuals with the outcome of interest divided by the person-years as contributed by the population at risk of the outcome of interest during the study period. Follow-up is censored at the earliest occurrence of the following: the outcome of interest, loss to follow-up, death, or the end of the observation period. For treatment cohorts, follow-up is additionally censored six months after treatment discontinuation or a switch to another treatment. Incidence rates will be presented per 1,000 PYs together with 95% Poisson confidence intervals. **Figure 1** represents an example of incidence rate estimation.

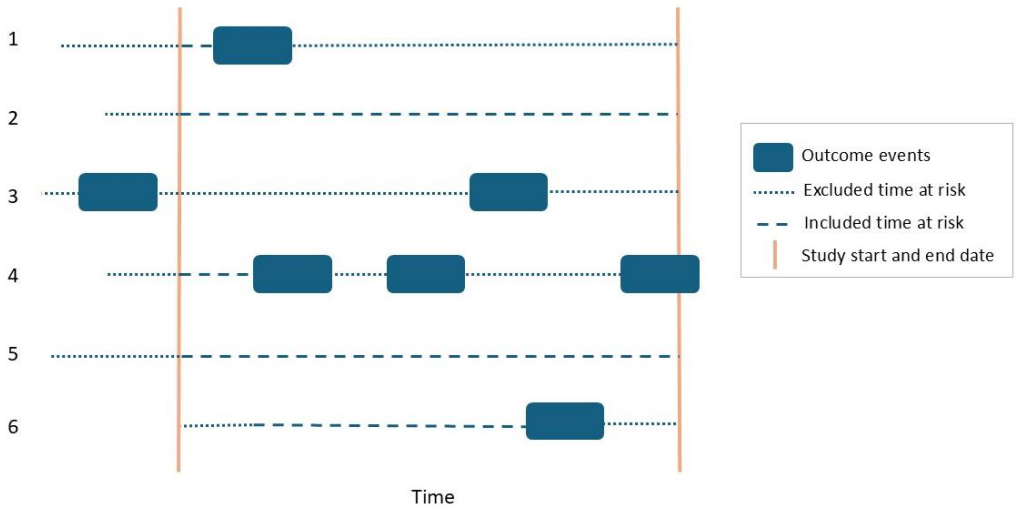


Figure 1. Examples of incidence rate estimation.

Patient IDs 1 and 4 contributed time at risk between the study start until they have an incident outcome of interest. Patient IDs 2 and 5 contributed time at risk between the study start and end date as no outcome of interest was observed between this period nor before the study start date. Patient ID 6 contributed time at risk from date where he had enough history of data (365 days) until he had an incident outcome of interest. Individuals should not have had a history of the suicidality to ensure that only new instances of the events were captured for analysis. Patient ID 3 was excluded due to having a prior history of the suicidality-related event.

- Supplementary analyses:

Incidence rates will be stratified by:

- Age groups (18-30, 31-40, 41-50, 51-60, 61-70, 71+).
- History of psychiatric disorder

- History of sexual dysfunction
- Calendar year for the general population and follow-up year for indication and treatment cohorts note: For the general male population, the study entry date is random, allowing yearly incidence rates to be analysed by calendar year. However, for condition and treatment cohorts, follow-up time scale is more relevant, allowing one to look at how incidence rates change over time since the disease debut or treatment initiation.

8.8.6 Output

Output will include a PDF report including an executive summary, and the following table(s) and figure(s):

Main results:

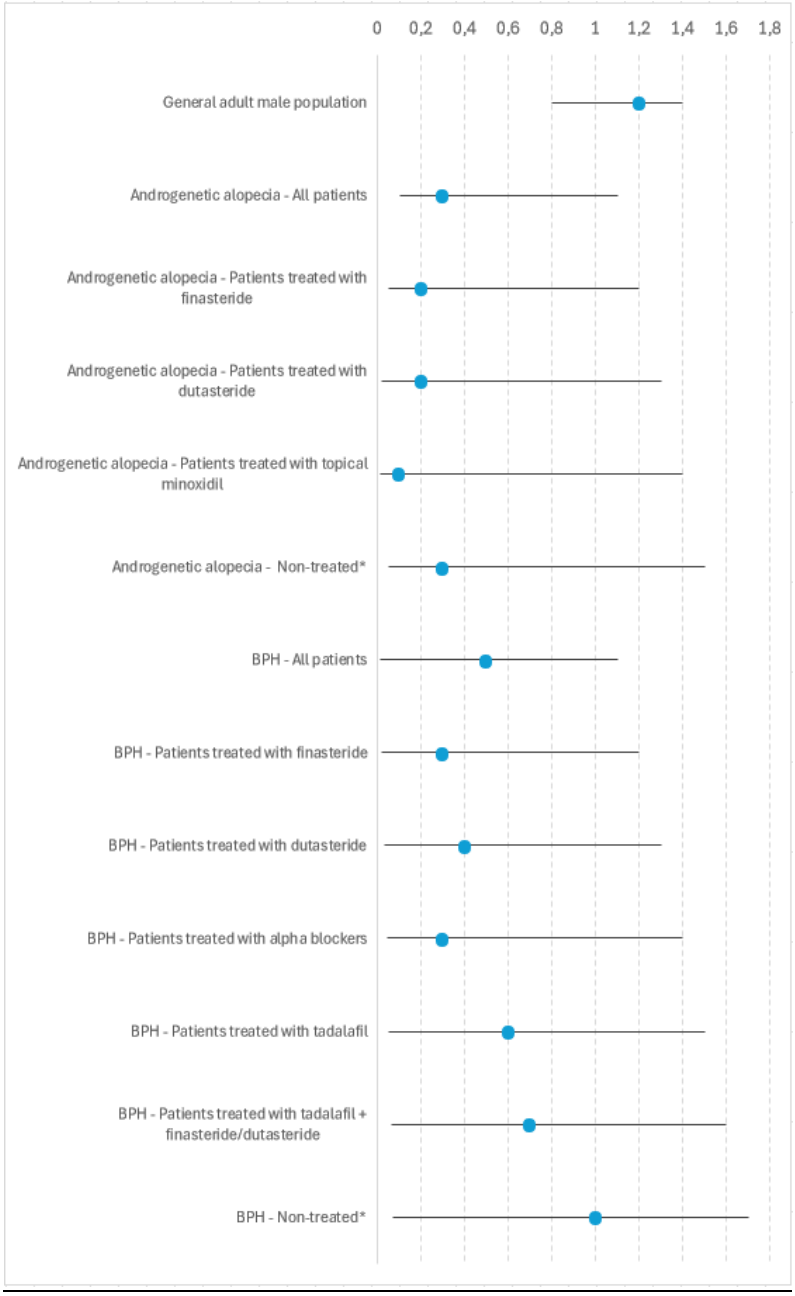
Table shell 1. Distribution of baseline characteristics among participants (number and %, median and IQR) per cohorts of interest by data source.

Database	Characteristic	General adult male population	Androgenetic alopecia (first ever) diagnosis	Finasteride for androgenetic alopecia	Dutasteride for androgenetic alopecia	Topical minoxidil for androgenetic alopecia	BPH (first ever) diagnosis	Finasteride for BPH	Dutasteride for BPH	Alpha blockers for BPH	Tadalafil for BPH	Tadalafil + finasteride/ Dutasteride for BPH
CPRD UK	N participants											
	Median age (IQR) at index date											
	Age groups, in year											
	18-30 31-40 41-50 51-60 61-70 71+											
	History of psychiatric disorder (%)											
	History of sexual dysfunction (%)											
	Median index year (IQR)											
IPCI												
etc.												

Table shells 2 to 8 (one for each data source)**.** Incidence rates of composite suicidality outcome per 1,000 person- years by indication and treatment.

Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
General adult male population						
Androgenetic alopecia						
All patients						
Patients treated with finasteride						
Patients treated with dutasteride						
Patients treated with topical minoxidil						
No treatment						
BPH						
All patients						
Patients treated with finasteride						
Patients treated with dutasteride						
Patients treated with alpha blockers						
Patients treated with tadalafil						
Patients treated with tadalafil + finasteride/dutasteride						
No treatment						

Figures 1 to 7: Each figure will depict the overall incidence rates (95% CI) for various cohorts, including the general population, the androgenetic alopecia cohort, and the treated androgenetic alopecia cohort (with a row representing each treatment), as well as the BPH cohort and the treated BPH cohort (with a row representing each treatment). Separate figures will be provided for each data source. Example is provided below.



* Non-treated represents patients who have not had a recorded prescription for the study treatments for each condition of interest.

Figure 1-7. Incidence rates (95% CI) of suicide-related events per 1,000 PYs in (X) database.

Appendixes

Appendix Tables S1-S42: Number of participants, total number of incident cases of suicide related events, follow up time (person-years), incidence rates per 1,000 PYs (95% CI) by indications and treatments will be

presented in tables for each data source. They will be stratified by age, by history of psychiatric disorders, by history of sexual dysfunction for each database as follows (example):

Tables S1- S7. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in androgenetic alopecia patients by treatment and by age group in [data source name].

Age group	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
18-30	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						
31-40	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						
Etc.							

Tables S8- S14. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in androgenetic alopecia patients by treatment and by history of psychiatric disorders in [data source name].

Psychiatric disorders	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
Yes	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						
No	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						

Tables S15- S21. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in androgenetic alopecia patients by treatment and by history of sexual dysfunction in [data source name].

Sexual dysfunction	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
Yes	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						
No	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with topical minoxidil						
	No treatment						

Tables S22- S28. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in BPH patients by treatment and by age group in [data source name].

Age group	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
18-30	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						
31-40	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						
Etc.							

Tables S29- S35. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in BPH patients by treatment and by history of psychiatric disorders in [data source name].

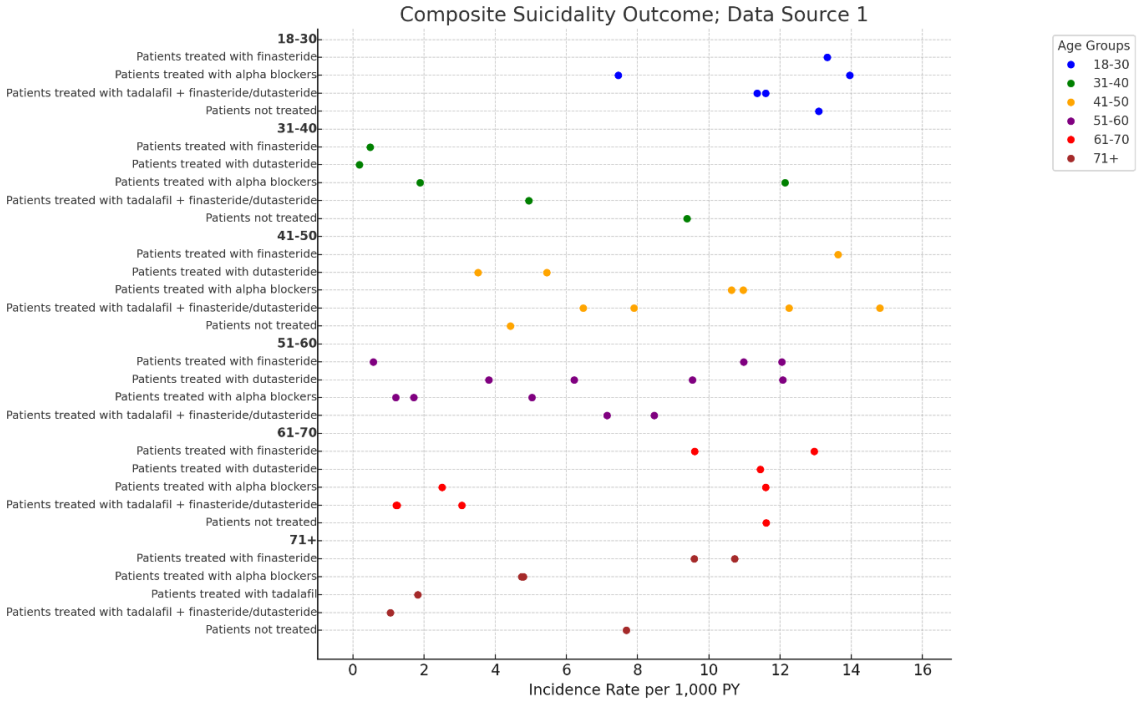
Psychiatric disorders	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
Yes	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						
No	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						

Tables S36- S42. Incidence rates (IR) of composite suicidality outcome per 1,000 person- years in BPH patients by treatment and by history of sexual dysfunction in [data source name].

Sexual dysfunction	Cohorts	N of participants	Follow-up (person-years)	N of incident outcome events	Incidence rates per 1,000 PYs	95% CI	
Yes	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						
No	All patients						
	Patients treated with finasteride						
	Patients treated with dutasteride						
	Patients treated with alpha blockers						
	Patients treated with tadalafil						
	Patients treated with tadalafil + finasteride/dutasteride						
	No treatment						

Appendix Figures S1-S7: Study attrition of individuals included in each cohort per database. Numbers of patients for each of the items described in the inclusion/exclusion criteria section will be displayed for the 7 data sources separately.

Appendix Figures S8-S21: will present the summarized incidence rates from Appendix Tables S1-S7 for androgenetic alopecia and Tables S22-S28 for BPH patient, stratified by age group and treatment across each data source. The X-axis will display incidence rates per 1,000 PYs (without 95% CI), while the Y-axis will represent age groups further stratified by treatments. Each dot will be coloured to correspond to a specific age category, with a legend provided to explain the colour scheme. Example is provided below.



Appendix Figures S22-S28: Incidence rates of the outcomes of interest over calendar years/follow-up years will be displayed for the general adult male population, adult male patients with incident androgenetic alopecia including treatment initiators nested cohorts, and adult male patients with incident BPH including treatment initiators nested cohorts. Separate figures will be provided for each data source.

They will be displayed separately for the general population, the indication and the treatment cohorts, since they have different time scales (calendar time for general population, follow-up time for the other cohorts). We will have 1 figure with three panels per data-source: (1) for the general population; (2) for the androgenetic alopecia indication cohort and each androgenetic alopecia treatment cohort (3) for the BPH indication cohort and each BPH treatment cohort. In figures 2 and 3, each cohort will be represented in a separate colour. Time scale will be on the horizontal axis and the incidence rates per 1,000 PYs will be on the vertical axis. Each year point estimate will be represented by a dot with whiskers indicating 95% confidence intervals. These dots can be connected by a trend line to illustrate variations in incidence rates over time.

Appendix Table S43. Contribution of individual suicide related events to the composite suicidality outcome.

Database	Cohorts	Completed suicide N (%)	Attempted suicide N (%)	Suicidal ideation N (%)	Intentional self-harm N (%)
CPRD Gold	**General adult male population**				
	Androgenetic alopecia				
	All patients				
	Patients treated with finasteride				
	Patients treated with dutasteride				
	Patients treated with topical minoxidil				
	No treatment				
	BPH				
	All patients				
	Patients treated with finasteride				
	Patients treated with dutasteride				
	Patients treated with alpha blockers				
	Patients treated with tadalafil				
	Patients treated with tadalafil + finasteride/dutasteride				
	No treatment				
IPCI					
Etc					

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 database. No meta-analysis of results will be conducted.

9. DATA MANAGEMENT

9.1 Data management

All databases 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 standardized analytics wherever possible. Each data partner will execute the study code against their database 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.

9.2 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 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 Remote Research Environment. 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.

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 drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level. A pharmacist will review the codes of the <drug(s)> of interest.

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 databases contributing to the study and identify any codes potentially omitted in error.

The study code will be based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation 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.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data; therefore, data quality issues must be considered. In particular, the recording of the outcome events may vary across databases. While relatively few false positives would be expected, false negatives may be more likely, especially for databases without patient-level linkage to secondary care data. This is because the recording of completed suicide and suicide related events are often under-reported in primary care records because of various factors like social stigma, misclassification of cases (e.g., recorded as accidental), not admission in hospital, the prioritization of physical over mental health symptoms, and cultural attitudes. While linkage to death certification data could improve reporting, it would still fall short of a true "gold standard", as the deficiencies in coding suicide on death certificates are well documented.(41-45) It is not expected that any biases arising from incomplete ascertainment of outcomes would be differential.

Other limitations can impact on the results of study from routinely collected health care data. The under-recording of androgenetic alopecia in healthcare databases can significantly affect the validity of incidence rate estimates. Many individuals with androgenetic alopecia may not seek formal medical care, viewing it as a cosmetic issue, leading to incomplete capture of diagnoses in EHRs. In Spain, another challenge arises from the lack of reimbursement for oral or topical treatments for alopecia. This means that such treatments are not routinely captured in healthcare databases, potentially limiting the scope of data analysis for this condition and results in underestimations of the true prevalence of androgenetic alopecia. Additionally, the use of over the counter (OTC) treatments or medications like (topical) finasteride purchased online, will underestimate individuals exposed to the drug of interest. The potential off-label use of finasteride, particularly in men over 40, is another limitation in studies evaluating its effects. While commonly prescribed for androgenetic alopecia or BPH, it is also used for purposes beyond these indications, such as delaying hair loss or for anti-aging, which may not be accurately recorded in medical databases.

Furthermore, the COVID-19 pandemic (from 2020-2022) introduces a unique challenge. Changes in healthcare utilization patterns, routine clinical practices, and information recording during the pandemic might potentially distort estimates for the years 2020 and 2021. Disruptions in healthcare services and altered patient behaviours could influence the representation of suicide-related events data during this period. A significant increase in suicidal thoughts and behaviours was reported during the COVID-19 pandemic. Factors such as loneliness, anxiety, depression, financial instability, and reduced social support contributed to this increase. For instance, a meta-analysis found higher rates of suicidal ideation (10.81%), suicide attempts (4.68%), and self-harm (9.63%) during the pandemic compared to pre-pandemic levels.(46) Consequently, the results from this period will be interpreted with caution.

Additionally, the results estimated from this study will only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical purpose rather than primarily for research use. Consequently, using five primary care data sources from the UK, Spain, Denmark, Germany, Croatia, and the Netherlands limits generalisability to those countries.

While OMOP provides mappings to established vocabularies like SNOMED, inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data analysis in different databases. For example, in the current version of DK-DHR, a low number of BPH cases have been mapped to the OMOP CDM. These issues stem from specific coding practices in the local vocabularies. In DK-DHR, the vocabulary

is an adaptation of ICD-10, where BPH-related codes may not fully align with OMOP conventions. Outcome misclassification may also occur due to coding limitations. For instance, DK-DHR have counts for suicidality events recorded within the "condition" field, while observation-level mappings are incomplete. Furthermore, the German coding system, which serves as the basis for mappings, includes less specific codes for certain outcomes of interest, increasing the risk of misclassification in InGef RDB. These discrepancies are expected to be addressed through updates to ETL logic rules, anticipated in December 2024 updates.

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

All data sources require approval from their respective local Institutional Review Boards (IRB) to perform this study, with the exception of DK-DHR Denmark which will not require any further specific approvals to undertake this study.

14. 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.

15. OTHER ASPECTS

None.

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17. ANNEXES

Appendix I: – Concepts set for study variables

Conditions concept name and concept IDs definition is listed in the **Table S 1**.

Table S 1. Preliminary list of concept IDs for conditions exposure definition.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Androgenetic alopecia	Male pattern alopecia	4339092		SNOMED
BPH	Benign prostatic hyperplasia	198803		SNOMED
	Prostatism	4016155		SNOMED
	Prostatic obstruction	4188305		SNOMED

	Lower urinary tract symptoms due to benign prostatic hypertrophy	45770925		SNOMED
	Hyperplasia of prostate	197032		SNOMED
Mental health disorders	Depressive disorder	440383		SNOMED
	Depressed mood	40546087		
	Anxiety	441542		SNOMED
	Bipolar disorder	436665		SNOMED
	Eating disorder	439002	4143677, 46285098	SNOMED
	Psychotic disorder	436073		SNOMED
Sexual dysfunction	Psychosexual dysfunction	440068		SNOMED
	Sexual disorder	4335174		SNOMED
	Psychosexual disorder	436666		SNOMED

List of medicines concepts definition is provided in the **Table S 2**.

Table S 2. Preliminary list of concept IDs for treatments exposure definition.

Substance Name	Concept name	Ingredient Concept ID including descendants	Vocabulary
Finasteride	finasteride	996416	RxNorm
	finasteride delayed release oral tablet	43158527	RxNorm
	~~finasteride injectable solution~~	~~21092488~~	~~RxNorm~~
	finasteride oral capsule	35874759	RxNorm
	finasteride oral powder	40727856	RxNorm
	finasteride oral suspension	21112185	RxNorm
	finasteride oral tablet	40039832	RxNorm
Dutasteride	dutasteride	989482	RxNorm
	dutasteride / tamsulosin delayed release oral capsule	36269492	RxNorm
	dutasteride / tamsulosin extended-release oral capsule	43269047	RxNorm

	dutasteride / tamsulosin oral capsule	40222570	RxNorm
	dutasteride extended-release oral capsule	35766105	RxNorm
	dutasteride oral capsule	40033414	RxNorm
	dutasteride oral solution	21101685	RxNorm
	dutasteride oral tablet	2074253	RxNorm
Topical minoxidil	minoxidil topical foam	40134989	RxNorm
	minoxidil topical gel	40065459	RxNorm
	minoxidil topical lotion	40065460	RxNorm
	minoxidil topical ointment	41142871	RxNorm
	minoxidil topical powder	40743375	RxNorm
	minoxidil topical solution	40065461	RxNorm
	minoxidil topical spray	44818151	RxNorm
Alpha blockers	terazosin	1341238	RxNorm
	tamsulosin	924566	RxNorm
	silodosin	19012925	RxNorm
	alfuzosin	930021	RxNorm
	doxazosin	1363053	RxNorm
Tadalafil	tadalafil	1336926	RxNorm
	tadalafil delayed release oral tablet	43207191	RxNorm
	tadalafil oral capsule	1830694	RxNorm
	tadalafil oral suspension	741670	RxNorm
	tadalafil oral tablet	40102137	RxNorm
Tadalafil + finasteride	finasteride / tadalafil pill	702486	RxNorm

Outcomes concept name and concept IDs definition is listed in the **Table S 3.**

Table S 3. Preliminary list of concept IDs for outcome definition.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Suicide	Suicide	440925	4198985	SNOMED
Suicide attempt	Suicide attempt	4219484	4206010	SNOMED

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
	Injury due to suicide attempt	4257906		
	Self-administered poisoning	4181216		
	Intentional overdose	607149		
	Suicide deliberate poisoning	444362		
Suicide ideation	Threatening suicide	4216115	602870, 4190444	SNOMED
	Suicidal thoughts	4273391		
	Harmful thoughts	4037303		
	Feeling suicidal	4021339		
	At risk for suicide	4021336		
	Suicide risk	37399733		
	Suicide plan	600767		
Intentional self-harm	Self-inflicted injury	439235	440925, 42536693, 42573140, 42596336, 4206010, 42573949	SNOMED
	Self-destructive behaviour	608248		
	Late effect of self-inflicted injury	435446		
	Intentionally harming self	4303690		
	Suicide deliberate poisoning	444362		
	Self-administrated poisoning	4181216		
	Intentional overdose of prescription only medication	44802958		
	Intentional overdose	607149		
Composite Suicidality Outcome	Suicide	440925	4206010, 42596336, 42536693, 42573140, 42573949	SNOMED
	Suicide attempt	4219484		
	Injury due to suicide attempt	4257906		
	Suicidal thoughts	4273391		

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
	Harmful thoughts	4037303		
	Feeling suicidal	4021339		
	At risk for suicide	4021336		
	Suicide risk	37399733		
	Threatening suicide	4216115		
	Suicide plan	600767		
	Self-inflicted injury	439235		
	Self-destructive behaviour	608248		
	Late effect of self-inflicted injury	435446		
	Intentionally harming self	4303690		
	Self-administered poisoning	4181216		
	Intentional overdose	607149		
	Suicidal deliberate poisoning	444362		

Appendix II: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: DARWIN EU® - Suicidality after exposure to finasteride and dutasteride

EU PAS Register® number: n/a
Study reference number (if applicable): P3_C1-019

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[1]	☒	☐	☐	8.3
1.1.2 End of data collection[2]	☒	☐	☐	8.3
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.	☒	☐	☐	5

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 is the study conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
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)	☒	☐	☐	8.5
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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))	☐	☐	☒	

[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.

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)	☒	☐	☐	12

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
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	☒	☐	☐	8.5
	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)	☐	☐	☒	
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)	☐	☐	☒	
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)	☐	☐	☒	
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
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2
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)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.2

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?	☐	☐	☒	
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?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
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)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	10
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)	☒	☐	☐	8.7

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have the requirements of the 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?	☐	☐	☒	

Comments:

Appendix III: Additional Information

Name of the main author of the protocol: Marzyeh Amini

Date: 27/01/2025

Signature: *M. Amini*