Study Protocol

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DARWIN EU ® - Drug utilisation study in individuals with cystic fibrosis in Europe

Authors: Ellen Gerritsen, Dina Vojinovic

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<u>Study objectives</u>:

1. To describe treatment patterns of CFTR modulators at the active ingredient level, from the first recorded CFTR modulator treatment after CF diagnosis until end of follow up, including the proportion of individuals switching between CFTR modulators, overall and stratified by paediatric and adult populations.

2. To characterise individuals initiating CFTR modulator therapy, overall (any CFTR modulator) and by active ingredient, in terms of demographics, and use of other CF related therapies, overall and stratified by paediatric and adult populations.

3. To characterise CFTR modulator use, overall (any CFTR modulator) and by active ingredient, including treatment duration, cumulative dose, number of repeated prescriptions, overall and stratified by paediatric and adult populations.

4. To estimate the background incidence rates of pre-specified adverse events of special interest (cataract, depression, anxiety, and haemoptysis) in the CFTR modulator treated individuals, overall and by active ingredient level, presented overall and stratified by paediatric and adult populations and by calendar year.

5. To measure the incidence of pulmonary exacerbation following CFTR modulator initiation, overall (any CFTR modulator) and by active ingredient level, presented overall and stratified by paediatric and adult populations, and time since treatment initiation (one- and two-years</td></tr>
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	post-initiation).
Countries of study	France, United Kingdom, Spain, Germany, Norway, Italy
Author(s)	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
APHM	Assistance Publique – Hôpitaux de Marseille
ATC	Anatomical Therapeutic Chemical classification system
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CDM	Common Data Model
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CM	Clinical Modification
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DRE	Digital Research Environment
DOI	Declaration of interests
DQD	Data Quality Dashboard
DUS	Drug Utilisation Study
ED	Emergency Department
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUDA	European Union Drug Agency
GP	General Practitioner
GDPR	General Data Protection Regulation
H12O	Hospital Universitario 12 de Octubre
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Index date
IP	Inpatient
MA	Marketing Authorisation
NA	Not applicable
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OT	Other

PAS	Post-Authorization Studies
POLIMI	Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
PPIs	Proton-pump inhibitors
RCT	Randomised Controlled Trial
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
UDCA	Ursodeoxycholic acid
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug utilisation study in individuals with cystic fibrosis in Europe

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientist	Gargi Jadhav Isabella Kaczmarczyk	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
APHM	Dorian Grousset Vanessa Pauly Laurent Boyer	Assistance Publique – Hôpitaux de Marseille
CDWBordeaux	Guillaume Verdy	Centre Hospitalier Universite de Bordeaux
CPRD GOLD	Marta Pineda Moncusí Wai Yi Man Antonella Delmestri	University of Oxford
H12O	Paula Rubio Mayo Javier de la Cruz Juan Luis Cruz Bermúdez Noelia García Barrio	Fundación Investigación Biomédica Hospital 12 de Octubre
IQVIA DA Germany	Akram Mendez James Brash	IQVIA
NLHR	Hedvig Marie Egeland Nordeng Nhung Trinh Saeed Hayat	Norwegian Institute of Public Health
POLIMI	Gianluigi Galli	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

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

3. ABSTRACT

Title

DARWIN EU® – Drug utilisation study in individuals with cystic fibrosis in Europe

Rationale and background

Cystic fibrosis (CF) is a rare, life-limiting genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in multi-organ dysfunction primarily affecting the respiratory and gastrointestinal systems. While symptomatic treatments remain essential, recent advances in CFTR modulators represent a shift toward targeted therapies addressing the underlying protein defect. Emerging evidence highlights both clinical benefits and potential safety concerns, including psychiatric adverse effects. This study aims to generate real-world evidence on treatment utilisation and safety outcomes among individuals with a CF diagnosis across Europe.

Research question and objectives

Research question:

What are the real-world treatment patterns and safety outcomes among individuals with a cystic fibrosis (CF) diagnosis in Europe?

Study objectives:

1. To describe treatment patterns of CFTR modulators at the active ingredient level, from the first recorded CFTR modulator treatment after CF diagnosis until end of follow up, including the proportion of individuals switching between CFTR modulators, overall and stratified by paediatric and adult populations.
2. To characterise individuals initiating CFTR modulator therapy, overall (any CFTR modulator) and by active ingredient, in terms of demographics, and use of other CF related therapies, overall and stratified by paediatric and adult populations.
3. To characterise CFTR modulator use, overall (any CFTR modulator) and by active ingredient, including treatment duration, cumulative dose, number of repeated prescriptions, overall and stratified by paediatric and adult populations.
4. To estimate the background incidence rates of pre-specified adverse events of special interest (cataract, depression, anxiety, and haemoptysis) in the CFTR modulator treated individuals, overall (any CFTR modulator) and by active ingredient level, presented overall and stratified by paediatric and adult populations and by calendar year.
5. To measure the incidence of pulmonary exacerbation following CFTR modulator initiation, overall (any CFTR modulator) and by active ingredient, presented overall and stratified by paediatric and adult populations, and time since CFTR modulator initiation (one- and two-years post-initiation).

Methods

Study design

This retrospective cohort study aims to characterise the use of CFTR modulator therapy in individuals with a CF diagnosis. The study will describe patient-level treatment patterns, including switching between CFTR modulators (*objective 1*), characterise individuals initiating CFTR modulator treatment (*objective 2*), evaluate patient-level treatment utilisation by assessing treatment duration, cumulative dose, number of repeated prescriptions of CFTR modulator treatment (*objective 3*), and estimate the incidence of pre-specified adverse events of special interest (*objective 4*) and pulmonary exacerbation (*objective 5*).

Study period

1st January 2015 to 31st December 2024 (or latest date available).

Study population

New CFTR modulator user cohort (objectives 1–5): Patient-level drug utilisation and patient-level characterisation analyses will include all individuals with first recorded CFTR modulator treatment in the period between 1st January 2015 and 31st December 2024 (or latest date available) after CF diagnosis. To ensure adequate follow-up, only individuals with the first recorded CFTR modulator treatment at least 180 days prior to the end of data availability in each database will be included. Inclusion criteria require at least one year of data visibility prior to the date of first recorded CFTR modulator treatment and no prior use of CFTR modulator therapy. The one year prior data requirement will not hold for children <1 year of age.

Variables

Condition of interest: Cystic fibrosis (CF)

Medication of interest:

CFTR modulator therapy	WHO ATC classification code
Ivacaftor	R07AX02
Ivacaftor and lumacaftor	R07AX30
Ivacaftor and tezacaftor	R07AX31
Ivacaftor, tezacaftor, and elexacaftor	R07AX32

Supportive CF therapies:

Drug class	Drug	WHO ATC classification code
Bile acid preparations	Ursodeoxycholic acid	A05AA02
Pancreatic enzymes	Multienzymes (lipase, protease, etc.)	A09AA02
Mucolytics	Dornase alfa (desoxyribonuclease)	R05CB13
Mucolytics	Mannitol, acetylcysteine, ambroxol	R05CB
Selective beta-2-adrenoreceptor agonists	Salbutamol	R03AC
Aminoglycoside antibacterials	Tobramycin	J01GB01
Proton pump inhibitors	All ingredients	A02BC

Events of special interest: cataract, depression, anxiety, haemoptysis, and pulmonary exacerbation.

Data sources

1. Assistance Publique – Hôpitaux de Marseille (APHM), France
2. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Hospital Universitario 12 de Octubre (H12O), Spain
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Norwegian Linked Health Registry data (NLHR), Norway
7. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy

Statistical analysis

Descriptive characterisation will be performed at the patient level (*objective 1*). The index date is defined as the date of the first recorded CFTR modulator prescription during the study period following CF diagnosis. The number and percentage of individuals treated with each of the CFTR modulators (at the active ingredient level) after diagnosis of CF will be described, including the use of treatment combinations. Sunburst and Sankey diagrams will be used to visualise treatment patterns and sequences over time. The statistical analysis will be performed based on OMOP CDM mapped data using the *TreatmentPatterns* R package.

Patient demographics, including age and sex, will be evaluated at the date of the first recorded CFTR modulator prescription during the study period, following CF diagnosis, overall (any CFTR modulator) and by active ingredient level *(objective 2)*. Use of supportive CF therapies will be evaluated in the CFTR modulator treated cohort before the index date, at the index date and, across post-index time windows (e.g., any time prior to the index date, 365 days preceding the index date, at the index date, 1 to 30 days, 1 to 90 days, 1 to 365 days, and 1 day to the end of available follow-up). The results will be presented as numbers and proportions, overall (for any CFTR modulator treatment) and by active ingredient. This analysis will be conducted using *CohortCharacteristics* and *DrugUtilisation* R packages based on OMOP CDM mapped data.

Incidence rates of pre-specified adverse events of special interest will be estimated following CFTR modulator treatment initiation (overall (any CFTR modulator) and by active ingredient level) in individuals with CF (*objective 4*). These results will be expressed as the number of individuals with the newly diagnosed event of interest following CFTR modulator treatment initiation per 1,000 person-years of the individuals fulfilling the inclusion and exclusion criteria. Incidence rates will be stratified by calendar years. The statistical analyses will be performed based on OMOP CDM mapped data using the *IncidencePrevalence* R package.

Incidence rates of pulmonary exacerbation will be estimated following CFTR modulator treatment initiation (overall (any CFTR modulator) and by active ingredient level) in individuals with CF (*objective 5*). These results will be expressed as the number of individuals with pulmonary exacerbation following CFTR modulator treatment initiation per 1,000 person-years. Incidence rates will be calculated for consecutive yearly intervals since the CFTR modulator therapy initiation, overall (any CFTR modulator) and at active ingredient level, with a maximum follow-up period of 2 years. These statistical analyses will be performed based on OMOP CDM mapped data using the *IncidencePrevalence* R package.

Patient-level utilisation: Duration of CFTR modulator treatment (overall (any CFTR modulator) and by active ingredient level), cumulative dose, and number of or repeated prescriptions will be calculated and

summarised, providing the minimum, quartiles, and maximum, where available. This analysis will be conducted using the *DrugUtilisation* R package based on OMOP CDM mapped data *(objective 3)*.

Stratification and reporting: All results will be reported for the overall cohort and stratified by paediatric and adult populations.

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

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	August 2025
Creation of Analytical code	July/August 2025
Execution of Analytical Code on the data	September 2025
Draft Study Report	10th October 2025
Final Study Report	November 2025

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

6. RATIONALE AND BACKGROUND

Cystic fibrosis (CF) is a progressive genetic disorder associated with high rates of premature mortality. The condition primarily affects the lungs and digestive system but can also involve other organs. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a protein responsible for regulating the movement of chloride ions and water across epithelial cell membranes.[1] Dysfunction of this protein leads to the production of abnormally thick and sticky mucus in the lungs, and viscous digestive secretions in the gastrointestinal tract.[2, 3]

More than 2,000 genetic variants of CFTR have been identified. These are commonly grouped into six functional classes, reflecting different mechanisms of protein dysfunction. Broadly, mutations may lead to absent, misfolded, or unstable CFTR protein, or impair the protein's ability to reach the cell surface, or function as an effective chloride channel.

CF can be diagnosed via newborn screening (elevated immunoreactive trypsinogen [IRT]), or in individuals with suggestive clinical features in combination with a sweat chloride concentration >59 mmol/L and/or presence of two disease-causing CFTR genetic variants on two different alleles.[4]

Treatment options are aimed at treating symptoms that affect the respiratory system and the gastrointestinal tract (GIT), and at nutrition and electrolytes.[3] For example, mucolytic dornase alfa helps reduce airway mucus viscosity, while bile acid preparation ursodeoxycholic acid (UDCA) is used to manage CF related liver disease.[3, 5] Proton-pump inhibitors (PPIs) are commonly prescribed to manage gastroesophageal reflux.[6] Pancreatic enzyme replacement therapy comprising of lipases, proteases, and amylases is essential to prevent malnutrition due to pancreatic insufficiency.[3, 7]

Recent therapeutic advances have focused on correcting the underlying CFTR protein dysfunction through CFTR modulators and gene therapy.[1, 3] While some studies suggest that CFTR modulators may reduce pulmonary exacerbations and improve liver function, other evidence indicates a potential association with adverse effects, including pulmonary exacerbations, cataract, depression, and anxiety.[8, 9]

Given the evolving CF treatment landscape, there is a need for comprehensive epidemiological evidence to characterise real-world treatment patterns and adverse events. This study aims to describe treatment use and safety outcomes among individuals with a CF diagnosis across Europe.

7. RESEARCH QUESTION AND OBJECTIVES

Research question:

What are the real-world treatment patterns and safety outcomes among individuals with a cystic fibrosis (CF) diagnosis in Europe?

Study objectives:

1. To describe treatment patterns of CFTR modulators at the active ingredient level, from the first recorded CFTR modulator treatment after CF diagnosis until end of follow up, including the proportion of individuals switching between CFTR modulators, overall and stratified by paediatric and adult populations.
2. To characterise individuals initiating CFTR modulator therapy, overall (any CFTR modulator) and by active ingredient, in terms of demographics, and use of other CF related therapies, overall and stratified by paediatric and adult populations.
3. To characterise CFTR modulator use, overall (any CFTR modulator) and by active ingredient, including treatment duration, cumulative dose, number of repeated prescriptions, overall and stratified by paediatric and adult populations.
4. To estimate the background incidence rates of pre-specified adverse events of special interest (cataract, depression, anxiety, and haemoptysis) in the CFTR modulator treated individuals, overall (any CFTR modulator) and by active ingredient level, presented overall and stratified by paediatric and adult populations and by calendar year.
5. To measure the incidence of pulmonary exacerbation following CFTR modulator initiation, overall (any CFTR modulator) and by active ingredient, presented overall and stratified by paediatric and adult populations, and time since CFTR modulator initiation (one- and two-years post-initiation).

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

Table 1. Study objectives.

A. Study objectives 1, 2, and 3.

Objective:	**Objective 1**: To describe treatment patterns of CFTR modulators at the active ingredient level, from the first recorded CFTR modulator treatment after CF diagnosis until end of follow up, including the proportion of individuals switching between CFTR modulators, overall and stratified by paediatric and adult populations. **Objective 2:** To characterise individuals initiating CFTR modulator therapy, overall (any CFTR modulator) and by active ingredient, in terms of demographics and use of other CF related therapies, overall and stratified by paediatric and adult populations. **Objective 3:** To characterise CFTR modulator use, overall (any CFTR modulator) and by active ingredient, including treatment duration, cumulative dose, number of repeated prescriptions, overall and stratified by paediatric and adult populations.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	**New CFTR modulator user cohort (*objectives 1 – 3*)** All individuals with the first recorded CFTR modulator treatment in the period between 1st January 2015 and 31st December 2024 (or latest date available) after CF diagnosis. To ensure adequate follow-up, only individuals with the first recorded CFTR modulator treatment at least 180 days prior to the end of data availability in each database will be included. Inclusion criteria require at least one year of data visibility prior to the first recorded CFTR modulator treatment and no prior use of CFTR modulator therapy. The one year prior data requirement will not hold for children below 1 year of age.

Exposure:	CFTR modulators: ivacaftor; ivacaftor and lumacaftor; ivacaftor and tezacaftor; ivacaftor, tezacaftor, and elexacaftor
Comparator:	None
Outcome:	Not applicable
Time *(when follow up begins and ends):*	**New CFTR modulator user cohort (*objectives 1 – 3*)** Follow-up will start from the date of first recorded CFTR modulator treatment (index date) during the study period after CF diagnosis, among individuals who meet all inclusion criteria: 1) first recorded CFTR modulator treatment between 1st January 2015 and 31st December 2024 (or latest date available) after CF diagnosis, 2) first recorded CFTR modulator treatment record occurring at least 180 days prior to the end of data availability in the respective data source, 3) at least one year of data visibility prior to the date of first recorded CFTR modulator treatment (will not hold for children below 1 year of age), and 4) no recorded use of CFTR modulator therapy (at active ingredient level) preceding treatment initiation. The end of follow-up will be defined as the earliest of following: 1) end of CFTR modulator treatment (overall/at active ingredient level), 2) loss to follow-up, 3) end of data availability, 4) date of death, or 5) end of study period (31st December 2024).
Setting:	Primary care, registry, inpatient and outpatient specialist care setting using data from 7 data sources: APHM (France), CDWBordeaux (France), CPRD GOLD (UK), H120 (Spain), IQVIA DA Germany (Germany), NLHR (Norway), and POLIMI (Italy).
Main measure of effect:	Number and percentage of individuals receiving each CFTR modulator (active ingredient level and treatment combinations), overall and stratified by paediatric and adult populations. Sunburst and Sankey diagrams to visualise treatment patterns and sequences over time, overall and stratified by paediatric and adult populations. Percentage of individuals switching between CFTR modulators, overall and stratified by paediatric and adult populations. Age and sex at the date of new (incident) CFTR modulator prescription (overall and by active ingredient), presented overall and stratified by paediatric and adult populations. The number and proportion of individuals receiving other CF related therapies at CFTR modulator treatment initiation and across pre-specified time windows, overall and stratified by paediatric and adult populations. The results will be presented for any CFTR modulator treatment and each of the CFTR modulators at the active ingredient level. Treatment duration for CFTR modulator treatment (overall and by active ingredient level) expressed as minimum, quartiles, and maximum, overall and stratified by paediatric and adult populations. Cumulative dose for CFTR modulator treatment (overall and by active ingredient), expressed as minimum, quartiles and maximum, overall and stratified by paediatric and adult populations. Number of repeated prescriptions for CFTR modulator treatment (overall and by active ingredient level), expressed as minimum, quartiles, and maximum, overall and stratified by paediatric and adult populations.

B. Study objectives 4 and 5.

Objective:	**Objective 4**: To estimate the background incidence rates of pre-specified adverse events of special interest (cataract, depression, anxiety, and haemoptysis) in the CFTR modulator treated individuals, overall (any CFTR modulator) and by active ingredient level, presented overall and stratified by paediatric and adult populations and by calendar year. **Objective 5**: To measure the incidence of pulmonary exacerbation following CFTR modulator initiation, overall (any CFTR modulator) and by active ingredient, presented overall and stratified by paediatric and adult populations, and time since CFTR modulator initiation (one and two years post-initiation).
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	**New CFTR modulator user cohort (*objectives 4 – 5*)**: All individuals with first recorded CFTR modulator treatment between 1st January 2015 and 31st December 2024 (or latest date available) after a CF diagnosis. To ensure sufficient follow-up, only individuals with first recorded CFTR modulator treatment at least 180 days prior to the end of data availability in each database will be included. Eligible individuals must have at least one year of data visibility prior to first recorded CFTR modulator treatment and no prior use of CFTR modulator treatment at the ingredient level. This requirement of one year of prior data history will not hold for children <1 year of age.
Exposure:	CFTR modulators: ivacaftor; ivacaftor and lumacaftor; ivacaftor and tezacaftor; ivacaftor, tezacaftor, and elexacaftor.
Comparator:	None
Outcome:	Pre-specified adverse events of interest: cataract, depression, anxiety, and haemoptysis Pulmonary exacerbation
Time *(when follow up begins and ends):*	Follow-up will start from the date of the first recorded CFTR modulator treatment (index date) during the study period following the CF diagnosis, among individuals who meet all inclusion criteria: 1) first recorded CFTR modulator treatment between 1st January 2015 and 31st December 2024 (or latest date available) after CF diagnosis, 2) first recorded CFTR modulator treatment occurring at least 180 days prior to the end of data availability in the respective data source, 3) at least one year of data visibility prior to the date of first recorded CFTR modulator treatment (will not hold for children <1 year of age), and 4) no recorded use of CFTR modulator therapy (at active ingredient level) preceding treatment initiation. End of follow-up for each specific outcome will be defined as earliest of following: 1) end of CFTR treatment, 2) first occurrence of the specific outcome of interest after the CFTR modulator treatment initiation, 3) loss to follow-up, 4) end of data availability, 5) date of death, or 6) end of study period (31st December 2024). Adverse events of interest are not considered mutually exclusive.
Setting:	Primary care, registry, inpatient and outpatient specialist care setting using data from 7 data sources: APHM (France), CDWBordeaux (France), CPRD GOLD (UK), H120 (Spain), IQVIA DA Germany (Germany), NLHR (Norway), and POLIMI (Italy).
Main measure of effect:	Incidence rates of pre-specified adverse events will be estimated among individuals initiating CFTR modulator treatment following CF diagnosis. These rates will be calculated overall (any CFTR modulator) and by active ingredient level. Results will be expressed as the number of individuals with the newly diagnosed adverse event of interest per 1,000 person-years of individuals fulfilling the inclusion and exclusion criteria). Incidence rates will be reported overall and stratified by paediatric and adult populations and calendar year. Incidence rates of pulmonary exacerbation will be assessed among individuals initiating CFTR modulator treatment, overall (any CFTR modulator) and by active ingredient. Incidence rates will be expressed as the number of individuals with the newly diagnosed pulmonary exacerbation per 1,000 person-years of individuals fulfilling the inclusion and exclusion criteria. These will be stratified by paediatric and adult populations, and time since CFTR modulator therapy initiation (one and two years post initiation).

8. RESEARCH METHODS

8.1. Study type and study design

A cohort study will be conducted using routinely collected health data from 7 data sources. The study will comprise the following parts:

- Cohort analysis (*Objectives 1, 2, 4,* and *5*, Patient-level characterisation of treatment patterns in individuals with CF initiating CFTR modulator treatment, characterisation of CFTR modulator users, pre-specified adverse events of special interest, and pulmonary exacerbation in CFTR modulator users).
- New drug user cohort (*Objective 3*, Patient-level drug utilisation regarding treatment duration, cumulative dose, and repeated prescriptions).

8.2. Study setting and data sources

The study will be conducted using routinely collected data from 7 databases in 6 European Countries (4 EU countries, United Kingdom, and Norway). All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Assistance Publique – Hôpitaux de Marseille (APHM), France
2. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Hospital Universitario 12 de Octubre (H12O), Spain
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Norwegian Linked Health Registry data (NLHR), Norway
7. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy

For this study, we have selected 7 data sources that were considered fit for purpose from the databases available in the DARWIN EU® Database Catalogue. The selection process was based on several key criteria: the number of individuals diagnosed with CF, the number of individuals prescribed the CFTR modulator therapy, and geographical spread. Based on the feasibility assessment performed, the suggested databases have sufficient counts of individuals diagnosed with CF and CFTR modulator therapy.

Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2**.

When it came to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the *Achilles* tool, which systematically characterises the data and presents it in a dashboard format that is inspected. The generated data characteristics, such as age distribution, condition prevalence per year, data density, and measurement value distribution were compared against expectations for the data. Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility consistently across the data sources. In terms of relevance, more general-purpose diagnostic tools, *CohortDiagnostics* (https://github.com/darwin-eu-dev/CohortDiagnostics) and *DrugExposureDiagnostics* (https://darwin-eu.github.io/DrugExposureDiagnostics/), were developed. *CohortDiagnostic* R package evaluated phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provided additional insights

into cohort characteristics, record counts and index event misclassification. The *DrugExposureDiagnostics* R package assessed ingredient specific diagnostics for drug exposure records.

Furthermore, timeliness was guarded by extracting the release dates for each dataset in the network and monitoring when data were out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it was important to have a clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the *CdmOnboarding* (and *Achilles*) packages contained a 'data density' plot. This plot displayed the number of records per OMOP domain on a monthly basis. This allowed getting insights when data collection started, when new sources of data were added and until when data was included.

Table 2. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of data	Number of active subjects	Last observation period
France	APHM	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Specialist care, hospital inpatient care	EHR, claims, registries	0.25 million	12/2024
France	CDW Bordeaux	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Hospital outpatient care, inpatient care, and ICU	EHR	0.25 million	06/2025
United Kingdom	CPRD GOLD	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Primary care, hospital outpatient care, inpatient care	EHR	2.83 million	12/2024
Spain	H12O	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Hospital outpatient care, inpatient care	EHR, registry	0.29 million	08/2024
Germany	IQVIA DA Germany	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Primary care, outpatient specialist care	EHR	4.48 million	12/2024
Norway	NLHR	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Registry	Registry	6.95 million	12/2023
Italy	POLIMI	Database covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Hospital outpatient care, inpatient care	EHR	0.09 million	09/2024

APHM = Assistance Publique – Hôpitaux de Marseille; CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; H12O = Hospital Universitario 12 de Octubre; DA = Disease Analyzer; NLHR = Norwegian Linked Health Registry data; POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; EHR = Electronic Health Record.

Assistance Publique – Hôpitaux de Marseille (APHM), France

This data source includes all hospital stays across various care settings—acute care, psychiatric care, rehabilitation care, and home hospitalization—capturing approximately 300,000 stays annually. The database also captures comprehensive drug prescription and administration data, including UCD drug codes, ATC classifications, quantities, and dosages, managed through PHARMA software. Additionally, medical and paramedical notes, such as hospitalization reports, radiology, EEG, endoscopy, and consultation summaries, are recorded using AXIGATE software. Laboratory data, covering both prescriptions and test results, is also included.

Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).[10]

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

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.[11] The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.[11] 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.[12-14]

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

Hospital Universitario 12 de Octubre (H12O), Spain

The data source is mainly the Electronic Health Record of the Hospital Universitario 12 de Octubre. It contains information from the different health domains (laboratory, prescriptions, treatments, administrative, diagnoses, etc.). In addition, information is also obtained from other data sources such as the pathological anatomy system, which provides information about sample analysis, and the cost system, containing information on the cost associated with a contact with the hospital.

IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992.[15] This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

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

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.[16, 17]

Norwegian Linked Health Registry data (NLHR), Norway

Norway has a universal public health care system consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants. Many population-based health registries were established in the 1960s with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration, and emergency preparedness. The data source contains harmonized data from the following registries: the Medical Birth Registry of Norway, the Norwegian Prescription Registry), the Norwegian Patient Registry, Norway Control and Payment of Health Reimbursement, the Norwegian Surveillance System for Communicable Diseases, the Norwegian Immunisation Registry, the National Death Registry, and the National Registry. Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.

Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy

Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, known simply as Policlinico of Milan, is a general hospital that can count on important excellence in different areas of care with a strong interdisciplinary focus. Given its nature as IRCCS – Institute for Research, Hospitalization and Health Care - in addition to care, it carries out biomedical and health research activities of a clinical and translational nature, involving the rapid transfer of therapies from the laboratories to the bedside of the sick person. Currently the DWH contains data from Hospitalization, Outpatients visits, Laboratory test, Therapies, Radiology, Anatomic Pathology, and a REDCap instance for non-profit studies.

8.3. Study period

The study period will be from 1st January 2015 until the earliest of 31st December 2024 or the date of the last database update for each respective database (please see **Table 2** for more details on the last update for each database).

8.4. Follow-up

For objectives (*objectives 1 – 5*), study participants will be followed from the date of first recorded CFTR modulator treatment (index date) after CF diagnosis, among individuals who meet all inclusion criteria: 1) first recorded CFTR modulator treatment between 1st January 2015 and 31st December 2024 (or latest date available) after CF diagnosis, 2) first recorded CFTR modulator treatment occurring at least 180 days prior to the end of data availability in the respective data source, and 3) at least one year of data visibility prior to the date of first recorded CFTR modulator treatment (will not hold for children <1 year of age). End of follow-up will be defined as earliest of following: 1) end of CFTR modulator treatment (at active ingredient level), 2) loss to follow-up, 3) end of data availability, 4) date of death, or 5) end of study period (31st December 2024).

The operational definition of the index date and other primary time anchors are presented by means of Table *3*.

Table 3. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
Individuals initiating CFTR modulator treatment (overall and by active ingredient) (*objectives 1 – 5*)	Date of first recorded CFTR modulator treatment after CF diagnosis	Single entry	Incident	[-Inf, -1]	IP, OP, OT	RxNorm	n/a	CFTR modulator treatment of interest after CF diagnosis	n/a	n/a

CF = cystic fibrosis, CFTR = cystic fibrosis transmembrane conductance regulator;
[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable.

8.5. Study population with inclusion and exclusion criteria

The study population (*objectives 1 – 5)* will include individuals with first recorded CFTR modulator treatment in the period between 1st of January 2015 and 31st of December 2024 (or latest date available) after CF diagnosis. Only individuals with first recorded CFTR modulator treatment at least 180 days prior to the end of data availability in each database will be included. Eligible individuals must have at least one year of data visibility prior to the first recorded CFTR modulator treatment and no use of CFTR modulator treatment before the index date. This requirement of one year of prior data history will not hold for children below 1 year of age.

The operational definitions of the inclusion criteria are presented by means of **Table 4.**

For *objectives 4* and *5*, additional exclusion criteria will be applied on an event-specific basis. Individuals will be excluded from the analysis of a specific adverse event if they have a record of that condition within one year before the index date (*objective 4*). This includes:

- A SNOMED disease code for depression (for exclusion from the depression outcome), a SNOMED disease code for anxiety (for exclusion from the anxiety outcome), a SNOMED disease code for cataract (for exclusion from the cataract outcome), a SNOMED disease code for haemoptysis (for exclusion from the haemoptysis outcome).

Additionally, individuals with a SNOMED disease code of upper or lower respiratory tract infection, requiring treatment with antibiotics or antiviral medications within 30 days prior to the start of follow-up, will be excluded from the analysis of pulmonary exacerbation (*objective 5*).

Table 4. 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
Observational period in the data source during the period 01/01/2015–31/12/2024 (or the latest date available)	All individuals present in the data source in the period 2015–2024 (or the latest date available)	n/a	n/a	IP, OP, OT	n/a	n/a	All individuals in the data source	n/a	n/a
First recorded CFTR modulator therapy	Individuals with first recorded CFTR modulator treatment, with no prior use of CFTR modulators	After	[-Inf, -1]	IP, OP, OT	RxNorm	n/a	All individuals in the data source	n/a	n/a
Prior database history	Study participants are required to have at least one year of prior history observed before contributing observation time (except for children <1 year of age)	Prior	[-365, 0]	IP, OP, OT	n/a	n/a	New users of CFTR modulator therapy	n/a	n/a
CF diagnosis	Individuals with a record of CF diagnosis prior to initiation of CFTR modulator treatment	After	[-Inf, 0]	IP, OP, OT	SNOMED	n/a	New users of CFTR modulator therapy	n/a	n/a

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

8.6. Variables

8.6.1. Exposure/s

For this study, exposure of interest is the use (during the study period) of the following CFTR modulators:

- Ivacaftor
- Ivacaftor and lumacaftor
- Ivacaftor and tezacaftor
- Ivacaftor, tezacaftor, and elexacaftor

A preliminary code list is provided in **Annex I**.

Treatment patterns of the CFTR modulators will be described following the first recorded CFTR modulator therapy after CF diagnosis.

The operational definition of exposure is described by means of **Table 5.**

8.6.2. Outcome/s

For this study, the outcomes of interest are the pre-specified adverse events, including cataract, depression, anxiety, and haemoptysis, and pulmonary exacerbation. The preliminary code list is provided in **Annex I**. Phenotype of pre-specified adverse events will be determined following input from EMA.

To ensure only incident cases are captured, individuals will be excluded from the analysis of a specific adverse event if they have a record of that condition within one year prior to the start of follow-up (cataract, depression, anxiety, and haemoptysis) or within 30 days prior to start of follow-up (pulmonary exacerbation).

Depression, anxiety, cataract, and haemoptysis will be identified by presence of corresponding SNOMED condition codes.

Pulmonary exacerbations will be identified as the occurrence of any of the following:

- SNOMED disease code for CF pulmonary exacerbation;
- An outpatient or emergency visit with a respiratory diagnosis and prescription of systemic antibiotics (either IV or oral broad-spectrum) within ±7 days;
- Hospitalisation with a primary diagnosis of respiratory infection or CF-related lung disease.

The operational definition of the outcomes is presented in **Table 6.**

Table 5. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
CFTR modulators	Preliminary code list provided in Annex I	[-inf, -1]	[0, censor]	IP, OP, OT	RxNorm	n/a	All individuals in the data source during the study period with CF record	Previous use of CFTR modulator therapy	n/a	n/a

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

Table 6. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Pre-specified adverse events of interest	Preliminary code list provided in Annex I	Primary	Binary	[-365, -1]	IP, OP, OT	SNOMED	n/a	New users of CFTR modulator therapy	n/a	n/a
Pulmonary exacerbation	Preliminary code list provided in Annex I	Primary	Binary	[-30, -1]	IP, OP, OT	SNOMED	n/a	New users of CFTR modulator therapy	n/a	n/a

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

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

Covariates for stratification in the treatment patterns analyses (*objective 1*), characterisation of CFTR modulator initiators (*objective 2*), treatment use (*objective 3),* and estimation of incidence rates of pre-specified adverse events of interest (*objective 4*) and pulmonary exacerbation (*objective 5*) will include:

- Age groups: overall, paediatric (<18 years) and adult population (≥18 years) (*objectives 1–5*);
- Calendar year (*objective 4*);
- Yearly intervals post-index time since CFTR modulator initiation: one and two years after modulator initiation (*objective 5*).

For subgroup analyses for *objectives 1 – 5*, individuals aged <18 years at the time of CFTR modulator initiation will be included in the paediatric cohort, while individuals aged ≥18 years at the time of CFTR modulator initiation will be included in the adult cohort.

Other variables for patient characterisation of individuals initiating CFTR modulator therapy (*objective 2*) will include:

- Demographics: age and sex
- Supportive CF therapies:
    - Bile acid preparations (ursodeoxycholic acid),
    - Mucolytics (dornase alfa (desoxyribonuclease), mannitol, acetylcysteine, ambroxol),
    - Pancreatic enzymes (multienzymes (lipase, protease, etc.))
    - Selective beta-2-adrenoreceptor agonists (salbutamol)
    - Aminoglycoside antibacterials (tobramycin)
    - Proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexlansoprazole, dexrabeprazole, vonoprazan, tegoprazan, fexuprazan, ilaprazole, as well as combination products containing omeprazole, lansoprazole, or rabeprazole).

Demographics will be assessed at index date, while supportive CF therapies will be characterised at the index date, and across post-index time windows (e.g., any time prior to the index date, 365 days preceding the index date, at the index date, 1 to 30 days, 1 to 90 days, 1 to 365 days, and 1 day to the end of available follow-up). The operational definition of the covariates is described in **Table 7**.

Table 7 . Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics / validation	Source for algorithm
Demographics (age, sex)	Characterisation in terms of age and sex	Counts	At ID [0]	IP, OP, OT	SNOMED	n/a	First time users of CFTR modulator therapy	n/a	n/a
Supportive CF therapies	Characterisation in terms of other CF related therapies. Preliminary code list provided in Annex I	Counts	[-Inf, ID], [-365, ID], ID [0], [1, 30], [1, 90], [1, 365], [1, Inf]	IP, OP, OT	RxNorm	n/a	First time users of CFTR modulator therapy	n/a	n/a

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

8.7. Study size

No formal sample size calculation was conducted for this descriptive study, as the aim is to describe the treatment patterns and safety outcomes among individuals with a CF diagnosis, irrespective of sample size. Based on a preliminary feasibility assessment the expected number of CF person counts differs across data sources and ranges from 600 in H12O to 5,500 in IQVIA DA Germany, while the expected number of person counts for CFTR modulator treatment ranges from 100 in APHM, CDWBordeaux, CPRD GOLD, and H12O to 300 in NLHR.

8.8. Analysis

The type of analysis by study type is fixed, as can be observed in **Table 8**.

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

Study type	Study classification	Type of analysis
Patient-level characterisation	Off-the-shelf (C1)	• Patient-level treatment pattern • Characterisation of individuals initiating CFTR modulator therapy • Incidence rates of pre-specified outcomes in pre-specified time
Patient-level DUS	Off-the-shelf (C1)	• Patient-level drug utilisation (treatment duration, cumulative dose, number of repeated prescriptions)

8.8.2. Federated network analysis

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

The data partners locally execute the analytics against the OMOP CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

8.8.3. Patient privacy protection

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

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

R-packages

We will use the R package *TreatmentPatterns* (https://github.com/darwin-eu-dev/TreatmentPatterns) for the patient-level characterisation of treatment patterns including combination and sequence of therapy and *DrugUtilisation* (https://github.com/darwin-eu/DrugUtilisation) for the patient-level characterisation of CFTR modulator initiators and treatment utilisation analyses including treatment duration, cumulative dose and number of repeated prescriptions for each medication. Additionally, we will use *IncidencePrevalence* (https://github.com/darwin-eu/IncidencePrevalence) for incidence rates of pre-specified adverse events of special interest and pulmonary exacerbation.

Drug exposure calculations

Drug eras will be defined as follows: exposure starts at the date of the first prescription after a washout. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications: two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 1**, first row.

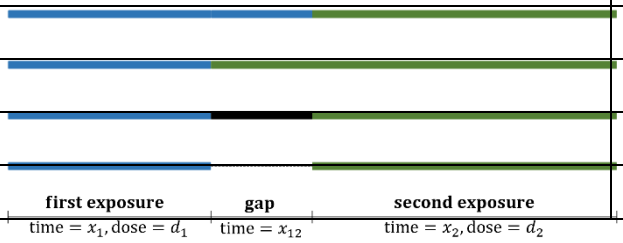
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 1. Gap era joint mode.

If two exposures overlap, the overlap time will be considered exposed to the first exposure (**Figure 2**). No time will be added at the end of the combined drug era to account for the overlap. If two exposures start at the same date, the overlapping period will be considered exposed to both. We will not consider repetitive exposure.

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

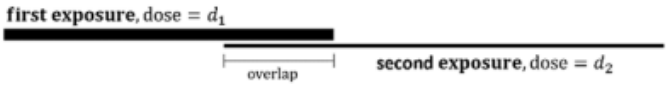


Figure 2. Gap era overlap mode.

Treatment patterns (*objective 1*), patient-level characterisation of CFTR modulator users (*objective 2),* and characterisation CFTR modulator treatment (*objective 3*)

The number and percentage of patients receiving each of the CFTR modulators at the active ingredient level, as well as treatment combinations, will be described overall and stratified by paediatric and adult populations (*objective 1*). Additionally, Sunburst plots and Sankey diagrams will be used to visualise treatment patterns and sequences over time. Sankey diagrams will be censored at end of treatment or end of follow-up as described in **Section 8.4**.

To construct treatment pathways, various parameters can be defined in the *TreatmentPatterns* package (**Figure 3**).

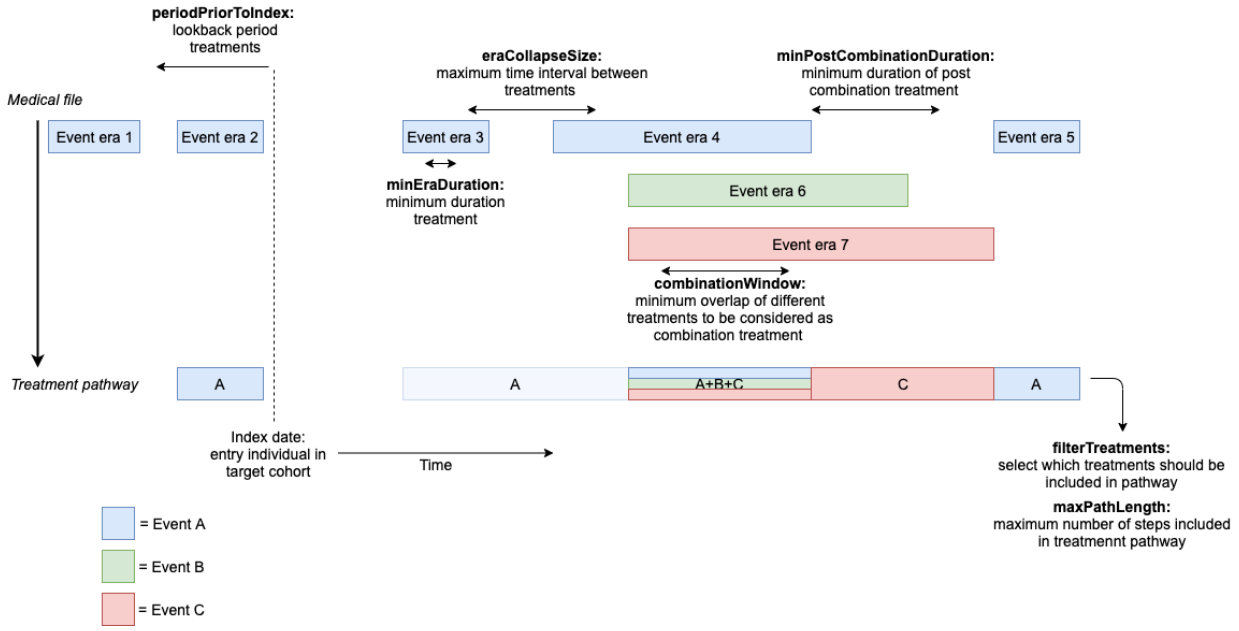


Figure 3. Parameters in *TreatmentPatterns* package

The preliminary parameters outlined in this study are described in **Table 9**. The target cohort refers to individuals with a diagnosis of CF, whereas event(s) refer to treatment(s) of interest.

Table 9. List of pathway settings with description and expected input.

Individual pathway settings		
periodPriorToIndex	The period (number of days) prior to the index date of the target cohort from which treatments should be included	0
minEraDuration	Minimum time an event era should last to be included in the analysis	0
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	30
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	30
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	30
filterTreatments	Select which treatments should be included in pathway: first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	All
maxPathLength	Maximum number of treatments included in pathway	5
Aggregate pathway settings		
minCellCount	Minimum number of persons with a specific treatment pathway for the pathway to be included in analysis	5

minCellMethod	Select to completely remove / sequentially adjust (by removing last step as often as necessary) treatment pathways below minCellCount	Adjust
groupCombinations	Select to group all non-fixed combinations in one category 'other' in the sunburst plot	TRUE
addNoPaths	Select to include untreated persons without treatment pathway in the sunburst plot	TRUE

For all CFTR modulator treatment initiators following CF diagnosis (*objective 2*), age and sex will be assessed at the date of first recorded CFTR modulator prescription (index date), overall (any CFTR modulator) and by active ingredient level. Use of other CF related therapies will be evaluated in the CFTR modulator treated cohort before the index date, at the index date, and across post-index time windows (any time prior to the index date, 365 days preceding the index date, at the index date, 1 to 30 days, 1 to 90 days, 1 to 365 days, and 1 day to the end of available follow-up). The results will be presented as numbers and proportions, overall (for any CFTR modulator treatment) and by active ingredient. Duration of CFTR modulator treatment (overall (any CFTR modulator) or by active ingredient level), cumulative dose, and number of repeated prescriptions for each medication (*objective* 3) will be calculated and summarised, providing the minimum, quartiles, and maximum, where available. The results will be presented overall and stratified by paediatric and adult populations. For databases where duration cannot be calculated, due to e.g., missing information on quantity or dosing, treatment duration will not be provided.

Background incidence rates of pre-specified adverse events (*objective 4*)

Incidence rates of pre-specified adverse events of special interest will be estimated following CFTR modulator treatment initiation in individuals with CF. The pre-specified events of interest are cataract, depression, anxiety, and haemoptysis. These incidence rates will be expressed as the number of individuals with the adverse event of interest following CFTR modulator treatment initiation after CF diagnosis per 1,000 person-years of the individuals fulfilling the inclusion and exclusion criteria. Incidence rates will be calculated overall and stratified by CFTR modulator active ingredient. Incidence rates will be reported overall and stratified by paediatric and adult populations and calendar year.

Incidence rates of pulmonary exacerbation (*objective 5*)

Incidence rates of newly diagnosed pulmonary exacerbation will be estimated among individuals initiating CFTR modulator treatment following CF diagnosis, overall and by active ingredient. The results will be expressed as the number of individuals with pulmonary exacerbation per 1,000 person-years of the individuals fulfilling the inclusion and exclusion criteria. Incidence rates will be calculated for consecutive yearly intervals since the initiation of CFTR modulator treatment (index date), with a maximum follow-up period of 24 months. Incidence rates will be stratified by paediatric and adult populations.

8.8.5. Methods to deal with missing data

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

8.8.6. Sensitivity analysis

To evaluate the robustness of analyses in the study population with first recorded CFTR modulator treatment, sensitivity analysis will be conducted across the data sources. This analysis will exclude the CFTR modulator treatment end as a censoring criterion *(objectives 4 and 5)*.

8.9. Evidence synthesis

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

9. DATA MANAGEMENT

9.1. Data management

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

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2. Data storage and protection

For this study, participants from various EU member states will process personal data from patients which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

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

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

Study specific quality control

When defining cohorts for medicinal products, a systematic search of possible codes for inclusion will be identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This

software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, *DrugExposureDiagnostics* will be run if needed to assess the use of different codes across the databases contributing to the study.

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

11. LIMITATIONS OF THE RESEARCH METHODS

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

General limitations:

Data sources/setting: This study utilises data from 7 sources: APHM, CDW Bordeaux, CPRD GOLD, H12O, IQVIA DA Germany, NLHR, and POLIMI. The results derived from these databases may not be representative of diagnoses and prescriptions in other countries or databases. Variations in results are expected across different countries and healthcare settings. Additionally, discrepancies may arise due to differences in how observation periods are handled across data sources. For instance, IQVIA DA Germany uses the last interaction with the healthcare system to define the end of the observation period. As a result, infrequent users may have shorter follow-up periods, decreasing the time at risk (i.e., the denominator) for incidence rate calculations. This could lead to an overestimation of incidence rates in the final months of the study period, as users are fully captured by the end of the study.

Drug prescriptions: A recorded prescription does not necessarily indicate that the patient actually took the drug. Therefore, assumptions of actual use are made.

Adverse events of special interest: The accuracy and consistency of recording of pre-defined adverse events of interest may vary across the data sources included in the study. Small counts may affect the analysis in some subgroups, as counts are not displayed for governance reasons when the number of events is <5.

Study period: Part of the study period coincided with the COVID-10 pandemic (2020–2022), which likely affects rates of outcomes due to changes in healthcare use.

Treatment duration: The completeness of treatment duration might be limited due to missing or incomplete records in some data sources. According to OMOP conventions, imputation of treatment duration (e.g., using a fixed 30-day supply) may be applied during the ETL process in some source data. However, no additional imputation was performed as part of this study, and we sued treatment duration as recorded in the data source. While this approach allows for consistency in analyses, it may introduce misclassification bias if the actual treatment durations differ substantially from the imputed values. Additionally, treatment duration may be underestimated when patients transition between care settings, as these changes are not always fully captured in the data.

Study-specific limitations:

Phenotype of pulmonary exacerbation: Outcome of interest is defined based on standard concept IDs. Diagnostic codes might not capture subclinical cases, often lack granularity on disease severity, and can vary across healthcare settings.

Sample size: Certain strata may have small sample sizes, particularly for CFTR modulators that have only recently been approved. Due to the limited time since approval and current treatment patterns, the number of patients receiving these specific therapies may be low.

TreatmentPatterns R package: The *TreatmentPatterns* R package is used to provide an overview of different treatment combinations over time. The settings for key parameters are crucial for defining possible treatment pathways, i.e., which treatment eras will be considered as a separate treatment, as a combination treatment, or will be excluded from the analysis. For example, setting the *combinationWindow* parameter (time that two event eras need to overlap to be considered a combination treatment) too high may exclude too many combination treatments, while setting it too low will increase the complexity of interpreting the possible treatment pathways, and may lead to censoring due to low person counts. Furthermore, if the *minPostCombinationDuration* parameter (minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment) is set higher than the *minEraDuration* parameter (minimum time an event era should last to be included in the analysis), an event era before or after a generated combination treatment might be excluded from the analysis while meeting the requirements for the minimum time an event era should last.

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

Some of the data sources require approval from their respective IRB board, except for IQVIA DA Germany, which will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1. Study report

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

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

15. OTHER ASPECTS

Not applicable.

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17. ANNEXES

ANNEX I. List of preliminary concept definitions

Preliminary list of concept definition for CF

Concept id	Concept Code	Concept Name	Exclude	Descendants
42538542	762270003	Atypical cystic fibrosis	-	Yes
42538541	762269004	Classical cystic fibrosis	-	Yes
441267	190905008	Cystic fibrosis	-	Yes
3189821	18770001000004108	Cystic fibrosis exacerbation	-	Yes
4341770	235978006	Cystic fibrosis of pancreas	-	Yes
254320	86555001	Cystic fibrosis of the lung	-	Yes
36714965	720401009	Cystic fibrosis with gastritis and megaloblastic anemia syndrome	-	Yes
193174	86092005	Cystic fibrosis with meconium ileus	-	Yes
434615	81423003	Cystic fibrosis without meconium ileus	-	Yes
4143529	426705001	Diabetes mellitus associated with cystic fibrosis	-	Yes
44808532	859041000000103	Exacerbation of cystic fibrosis	-	Yes
45769170	707766007	Exocrine pancreatic manifestation co-occurrent and due to cystic fibrosis	-	Yes
37110724	725052002	Fetal cystic fibrosis	-	Yes
37396320	716088000	Follicular hamartoma with alopecia and cystic fibrosis syndrome	-	Yes
3183290	13840001000004105	Pulmonary exacerbation cystic fibrosis	-	Yes
42538543	762271004	Subclinical cystic fibrosis	-	Yes

Preliminary list of concept definitions for CF treatments

CFTR regulators

Ivacaftor (WHO ATC R07AX02)

Concept id	Concept Code	Concept Name	Exclude	Descendants
1525625	2611459	ivacaftor 94 MG / lumacaftor 75 MG [ORKAMBI]	Yes	Yes
35898621	OMOP5042861	ivacaftor 75 MG / tezacaftor 50 MG [Symkevi]	Yes	Yes
35200184	2053518	ivacaftor 188 MG / lumacaftor 150 MG [ORKAMBI]	Yes	Yes
994767	OMOP4821281	ivacaftor 150 MG / tezacaftor 100 MG [Symkevi]	Yes	Yes
2937581	OMOP5154281	ivacaftor 150 MG / tezacaftor 100 MG [Symdeko]	Yes	Yes
46275585	1655930	ivacaftor 125 MG / lumacaftor 200 MG [ORKAMBI]	Yes	Yes
44119057	OMOP1113688	ivacaftor 125 MG / lumacaftor 200 MG [Orkamb]	Yes	Yes
1718095	1812469	ivacaftor 125 MG / lumacaftor 100 MG [ORKAMBI]	Yes	Yes
963953	1999385	ivacaftor / tezacaftor Pill	Yes	Yes
963952	1999384	ivacaftor / tezacaftor Oral Product	Yes	Yes
36248597	1655925	ivacaftor / lumacaftor Pill	Yes	Yes
36248596	1655924	ivacaftor / lumacaftor Oral Product	Yes	Yes
35200175	2053507	ivacaftor / lumacaftor Granule Product	Yes	Yes
36787864	OMOP4776127	ivacaftor / lumacaftor Delayed Release Oral Tablet	Yes	Yes
42709323	1243041	ivacaftor	-	Yes
36953601	OMOP5184428	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG [Kaftrio]	Yes	Yes
2937578	OMOP5154278	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Trikafta]	Yes	Yes
35898626	OMOP5042866	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Kaftrio]	Yes	Yes
37497449	2257008	elexacaftor / ivacaftor / tezacaftor Pill	Yes	Yes
37497450	2257009	elexacaftor / ivacaftor / tezacaftor Oral Tablet	Yes	Yes
37497448	2257007	elexacaftor / ivacaftor / tezacaftor Oral Product	Yes	Yes

1200984	2635012	elexacaftor / ivacaftor / tezacaftor Oral Granules	Yes	Yes
1200983	2635011	elexacaftor / ivacaftor / tezacaftor Granule Product	Yes	Yes

Ivacaftor and lumacaftor (WHO ATC R07AX30)

Concept id	Concept Code	Concept Name
36787864	OMOP4776127	ivacaftor / lumacaftor Delayed Release Oral Tablet
36787863	OMOP4776126	ivacaftor / lumacaftor Delayed Release Oral Tablet [ORKAMBI]
35200175	2053507	ivacaftor / lumacaftor Granule Product
35200176	2053508	ivacaftor / lumacaftor Oral Granules
35200178	2053510	ivacaftor / lumacaftor Oral Granules [ORKAMBI]
36248596	1655924	ivacaftor / lumacaftor Oral Product
46275582	1655926	ivacaftor / lumacaftor Oral Tablet
44031018	OMOP1025649	ivacaftor / lumacaftor Oral Tablet [Orkamb]
46275586	1655931	ivacaftor / lumacaftor Oral Tablet [ORKAMBI]
36248597	1655925	ivacaftor / lumacaftor Pill
35200177	2053509	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules
35200180	2053512	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules [ORKAMBI]
36064779	OMOP4991020	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules [ORKAMBI] Box of 56
36064778	OMOP4991019	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules [ORKAMBI] Box of 56 by Vertex
36064780	OMOP4991021	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules [ORKAMBI] by Vertex
36064781	OMOP4991022	ivacaftor 125 MG / lumacaftor 100 MG Oral Granules Box of 56
1718094	1812468	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet
1718096	1812470	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet [ORKAMBI]
37592608	OMOP4782054	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet [ORKAMBI] Box of 112

36064782	OMOP4991023	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet [ORKAMBI] Box of 112 by Vertex
36064783	OMOP4991024	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet [ORKAMBI] by Vertex
37592607	OMOP4782053	ivacaftor 125 MG / lumacaftor 100 MG Oral Tablet Box of 112
36787862	OMOP4776125	ivacaftor 125 MG / lumacaftor 200 MG Delayed Release Oral Tablet
36787860	OMOP4776123	ivacaftor 125 MG / lumacaftor 200 MG Delayed Release Oral Tablet [ORKAMBI]
36787859	OMOP4776122	ivacaftor 125 MG / lumacaftor 200 MG Delayed Release Oral Tablet [ORKAMBI] Box of 112
36787858	OMOP4776121	ivacaftor 125 MG / lumacaftor 200 MG Delayed Release Oral Tablet [ORKAMBI] Box of 112 by Vertex
36787861	OMOP4776124	ivacaftor 125 MG / lumacaftor 200 MG Delayed Release Oral Tablet Box of 112
46275583	1655928	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet
44047453	OMOP1042084	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [Orkamb]
44127896	OMOP1122527	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [Orkamb] by Vertex
46275587	1655934	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [ORKAMBI]
21129850	OMOP344839	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [ORKAMBI] Box of 112
21129851	OMOP344840	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [ORKAMBI] Box of 112 by Vertex
41094107	OMOP2292069	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [ORKAMBI] Box of 56
21139766	OMOP344838	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet [ORKAMBI] by Vertex
21071175	OMOP344836	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet Box of 112
41179000	OMOP2376962	ivacaftor 125 MG / lumacaftor 200 MG Oral Tablet Box of 56
35200183	2053517	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules
35200185	2053519	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules [ORKAMBI]
36064775	OMOP4991016	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules [ORKAMBI] Box of 56
36064774	OMOP4991015	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules [ORKAMBI] Box of 56 by Vertex
36064776	OMOP4991017	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules [ORKAMBI] by Vertex
36064777	OMOP4991018	ivacaftor 188 MG / lumacaftor 150 MG Oral Granules Box of 56
1525624	2611458	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules

1525626	2611460	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules [ORKAMBI]
36932711	OMOP5194707	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules [ORKAMBI] Box of 56
36955827	OMOP5194708	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules [ORKAMBI] Box of 56 by Vertex
36949839	OMOP5194706	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules [ORKAMBI] by Vertex
36965398	OMOP5194704	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules Box of 56
35200179	2053511	ORKAMBI Granule Product
36248598	1655932	ORKAMBI Oral Product
36248599	1655933	ORKAMBI Pill

Ivacaftor and tezacaftor (WHO ATC R07AX31)

Concept id	Concept Code	Concept Name
963952	1999384	ivacaftor / tezacaftor Oral Product
963954	1999386	ivacaftor / tezacaftor Oral Tablet
2937582	OMOP5154282	ivacaftor / tezacaftor Oral Tablet [Symdeko]
42615249	OMOP5158302	ivacaftor / tezacaftor Oral Tablet [Symdeko]
994766	OMOP4821280	ivacaftor / tezacaftor Oral Tablet [Symkevi]
963953	1999385	ivacaftor / tezacaftor Pill
2937581	OMOP5154281	ivacaftor 150 MG / tezacaftor 100 MG [Symdeko]
994767	OMOP4821281	ivacaftor 150 MG / tezacaftor 100 MG [Symkevi]
963955	1999387	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet
2937580	OMOP5154280	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet [Symdeko]
994768	OMOP4821282	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet [Symkevi]
994769	OMOP4821283	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet [Symkevi] Box of 28
36074031	OMOP4982896	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet [Symkevi] Box of 28 by Vertex

36074032	OMOP4982897	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet [Symkevi] by Vertex
994770	OMOP4821284	ivacaftor 150 MG / tezacaftor 100 MG Oral Tablet Box of 28
35898621	OMOP5042861	ivacaftor 75 MG / tezacaftor 50 MG [Symkevi]
1360934	2174387	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet
35898619	OMOP5042859	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Symkevi]
35898617	OMOP5042857	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Symkevi] Box of 28
35898616	OMOP5042856	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Symkevi] Box of 28 by Vertex
35898618	OMOP5042858	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Symkevi] by Vertex
35898620	OMOP5042860	ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet Box of 28

Ivacaftor, tezacaftor and elexacaftor (WHO ATC R07AX32)

Concept id	Concept Code	Concept Name
1200983	2635011	elexacaftor / ivacaftor / tezacaftor Granule Product
1200984	2635012	elexacaftor / ivacaftor / tezacaftor Oral Granules
37497448	2257007	elexacaftor / ivacaftor / tezacaftor Oral Product
37497450	2257009	elexacaftor / ivacaftor / tezacaftor Oral Tablet
35898627	OMOP5042867	elexacaftor / ivacaftor / tezacaftor Oral Tablet [Kaftrio]
2937579	OMOP5154279	elexacaftor / ivacaftor / tezacaftor Oral Tablet [Trikafta]
42615250	OMOP5158303	elexacaftor / ivacaftor / tezacaftor Oral Tablet [Trikafta]
37497449	2257008	elexacaftor / ivacaftor / tezacaftor Pill
35898626	OMOP5042866	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Kaftrio]
2937578	OMOP5154278	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Trikafta]
1200988	2635024	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Granules
37497451	2257011	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet

35898625	OMOP5042865	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Kaftrio]
35898623	OMOP5042863	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Kaftrio] Box of 56
35898622	OMOP5042862	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Kaftrio] Box of 56 by Vertex
35898624	OMOP5042864	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Kaftrio] by Vertex
2937534	OMOP5154277	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet [Trikafta]
35888543	OMOP5036111	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet Box of 56
35888542	OMOP5036110	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet Box of 56 by Vertex
35888544	OMOP5036112	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG Oral Tablet by Vertex
36953601	OMOP5184428	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG [Kaftrio]
1537086	2557214	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet
36949100	OMOP5184430	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet [Kaftrio]
36933296	OMOP5184432	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet [Kaftrio] Box of 56
36948009	OMOP5184433	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet [Kaftrio] Box of 56 by Vertex
36928437	OMOP5184431	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet [Kaftrio] by Vertex
36949618	OMOP5184429	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG Oral Tablet Box of 56
1200985	2635013	elexacaftor 80 MG / ivacaftor 60 MG / tezacaftor 40 MG Oral Granules

Bile acid preparations

Ursodeoxycholic acid (ATC WHO A05AA02)

Concept id	Concept Code	Concept Name	Exclude	Descendants
21600513	A05AA02	ursodeoxycholic acid; oral	-	Yes

Mucolytics

Dornase alfa (desoxyribonuclease) (WHO ATC R05CB13), mannitol, acetylcysteine, ambroxol (R05CB)

Concept id	Concept Code	Concept Name	Exclude*	Descendants
40254176	R05CB16	mannitol; inhalant	-	Yes
21603392	R05CB13	dornase alfa (desoxyribonuclease); inhalant	-	Yes
21603385	R05CB06	ambroxol; oral	-	Yes
21603380	R05CB01	acetylcysteine; inhalant, oral	-	Yes

*Topical and ophthalmic concept ids were excluded.

Pancreatic enzymes

Multienzymes (lipase, protease etc.) (WHO ATC A09AA02)

Concept id	Concept Code	Concept Name	Exclude	Descendants
21600701	A09AA02	multienzymes (lipase, protease etc.)	-	Yes

*Topical concept ids were excluded.

Proton-pump inhibitors (PPIs) (WHO ATC A02BC)

Concept id	Concept Code	Concept Name	Exclude	Descendants
21600095	A02BC	Proton pump inhibitors	-	Yes

Aminoglycoside antibacterials - tobramycin (WHO ATC J01GB01)

Concept id	Concept Code	Concept Name	Exclude*	Descendants
21602995	J01GB01	tobramycin	-	Yes

Selective beta-2-adrenoreceptor agonists - salbutamol (WHO ATC R03AC02)

Concept id	Concept Code	Concept Name	Exclude	Descendants
21603256	R03AC02	salbutamol; inhalant	-	Yes

Preliminary list of concept definitions for pre-specified adverse event of interest

Cataract

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
4006784	Adherent cataract	37396246	Wellesley Carman French syndrome
760554	Age-related cataract of left eye	36675714	Warburg micro syndrome
765357	Age-related cataract of right eye	376401	Traumatic cataract
765527	Age-related nuclear cataract of left eye	374642	Total traumatic cataract
764824	Age-related nuclear cataract of right eye	36713803	Spondyloepiphyseal dysplasia, craniosynostosis, cleft palate, cataract and intellectual disability syndrome
4199963	Anterior subcapsular cataract	37117168	Spinal muscular atrophy, Dandy-Walker malformation, cataract syndrome
761591	Anterior subcapsular cataract of bilateral eyes	36715408	Siegler Brewer Carey syndrome
765242	Anterior subcapsular cataract of left eye	4102697	Rubella cataract
761590	Anterior subcapsular cataract of right eye	604912	Pulverulent cataract
372315	Anterior subcapsular polar cataract	36676675	Porencephaly, microcephaly, bilateral congenital cataract syndrome
761588	Anterior subcapsular polar cataract of left eye	380101	Partial resolved traumatic cataract
761589	Anterior subcapsular polar cataract of right eye	4048386	Osteogenesis imperfecta, recessive perinatal lethal, with microcephaly AND cataracts
375256	Anterior subcapsular polar senile cataract	37396376	Nathalie syndrome
37208215	Anterior subcapsular polar senile cataract of left eye	40482880	Nance-Horan syndrome
37208216	Anterior subcapsular polar senile cataract of right eye	4157030	Mittendorf dot
4105159	Atopic cataract	36675066	Microcornea, rod-cone dystrophy, cataract, posterior staphyloma syndrome
4007451	Axial cataract	36716389	Martsolf syndrome
37108933	Bilateral after-cataract not obscuring vision	4216348	Marinesco-Sjögren syndrome
760555	Bilateral age-related cataract	380722	Localized traumatic opacity
764823	Bilateral age-related nuclear cataracts	3655645	Localized cataract opacities due to and following traumatic injury
3662352	Bilateral anterior subcapsular polar cataract	37396247	Karandikar Maria Kamble syndrome

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
37209532	Bilateral anterior subcapsular polar senile cataract of eyes	36716448	Juvenile cataract, microcornea, renal glucosuria syndrome
3657141	Bilateral cataract of eyes caused by drug	4161420	Juvenile cataract
4317977	Bilateral cataracts	37111654	Intellectual disability, cataract, calcified pinna, myopathy syndrome
36684804	Bilateral cortical age-related cataract eyes	36716124	Intellectual disability with cataract and kyphosis syndrome
36684796	Bilateral eye brunescent cataract	4220818	Infantile cataract
37208008	Bilateral hypermature senile cataracts of eyes	45770919	Infantile and/or juvenile cataract
764825	Bilateral incipient cataracts	36715527	Hypergonadotropic hypogonadism with cataract syndrome
36684803	Bilateral posterior subcapsular polar senile cataract of eyes	45765456	Hyperferritinemia cataract syndrome
37208009	Bilateral senile combined form cataracts of eyes	36715372	Hydrocephalus with endocardial fibroelastosis and cataract syndrome
36684736	Brunescent cataract of left eye	604630	Hutterite type cataract
36684670	Brunescent cataract of right eye	36680594	Foveal hypoplasia with presenile cataract syndrome
4001501	Calcified cataract	1340287	Exacerbation of congenital cataract
4070183	Capsular cataract	1340271	Exacerbation of cataract
375545	Cataract	434145	Embryonal nuclear cataract
376979	Cataract due to diabetes mellitus	36716390	Crome syndrome
4225656	Cataract due to diabetes mellitus type 1	619198	Coralliform cataract
4221495	Cataract due to diabetes mellitus type 2	4068699	Congenital zonular cataract
609308	Cataract due to drug induced diabetes mellitus	4105600	Congenital total cataract
36713528	Cataract due to idiopathic hypoparathyroidism	4099981	Congenital sutural cataract
381566	Cataract due to inflammatory disorder	381392	Congenital subcapsular cataract
36713529	Cataract due to pseudohypoparathyroidism	37207888	Congenital posterior subcapsular polar cataract of right eye

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
4334867	Cataract following rupture of capsule	37207948	Congenital posterior subcapsular polar cataract of left eye
4334869	Cataract in hypoparathyroidism	45757716	Congenital posterior subcapsular polar cataract
4334868	Cataract in systemic disorders	4102696	Congenital posterior polar cataract
761598	Cataract of bilateral eyes due to inflammatory disorder	4100889	Congenital polar cataract
37311301	Cataract of left eye	3656920	Congenital nuclear cataract of right eye
3656946	Cataract of left eye caused by corticosteroid	3657007	Congenital nuclear cataract of left eye
35625718	Cataract of left eye due to diabetes mellitus	37395848	Congenital muscular dystrophy with infantile cataract and hypogonadism syndrome
761596	Cataract of left eye due to inflammatory disorder	4069803	Congenital membranous cataract
761595	Cataract of left eye due to ocular disease	4069800	Congenital lamellar cataract
765241	Cataract of lens capsule of bilateral eyes	3657139	Congenital cortical cataract of right eye
761582	Cataract of lens capsule of left eye	3657138	Congenital cortical cataract of left eye
765090	Cataract of lens capsule of right eye	4280227	Congenital cortical cataract
36712947	Cataract of posterior subcapsule of bilateral eyes	45770920	Congenital combined form cataract
36712946	Cataract of posterior subcapsule of left eye	36676498	Congenital cataract, progressive muscular hypotonia, hearing loss, developmental delay syndrome
36712945	Cataract of posterior subcapsule of right eye	36713473	Congenital cataract, hypertrophic cardiomyopathy, mitochondrial myopathy syndrome
37311300	Cataract of right eye	36676682	Congenital cataract, hearing loss, severe developmental delay syndrome
3656862	Cataract of right eye caused by corticosteroid	36716388	Congenital cataract with hypertrichosis and intellectual disability syndrome
35625717	Cataract of right eye due to diabetes mellitus	36716387	Congenital cataract with deafness and hypogonadism syndrome
761597	Cataract of right eye due to inflammatory disorder	36714026	Congenital cataract with ataxia and deafness syndrome
761594	Cataract of right eye due to ocular disease	36684665	Congenital cataract of right eye
376973	Cataract secondary to ocular disease	36684731	Congenital cataract of left eye

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
372624	Cataract with neovascularization	37116290	Congenital cataract ichthyosis syndrome
4301387	Cataracta brunescens	380513	Congenital cataract
4219330	Combined form of nonsenile cataract	443791	Congenital capsular cataract
376400	Combined form of senile cataract	4070185	Congenital blue dot cataract
4334129	Concussion cataract	37310630	Congenital anterior subcapsular polar cataract of right eye
37111463	Coronary age-related cataract	37310640	Congenital anterior subcapsular polar cataract of left eye
4008296	Coronary cataract	45757718	Congenital anterior subcapsular polar cataract
36684802	Cortical age-related cataract of left eye	4100720	Congenital anterior polar cataract
36684801	Cortical age-related cataract of right eye	37395915	Cochleosaccular degeneration and cataract syndrome
378534	Cortical and zonular cataract	37111650	Cataract, congenital heart disease, neural tube defect syndrome
4103579	Cortical cataract	36684615	Cataract of right eye due to and following trauma
44783428	Cortical nonsenile cataract	36684678	Cataract of left eye due to and following trauma
432895	Cortical senile cataract	36713858	Cataract glaucoma syndrome
4225524	Corticosteroid induced cataract	377864	Cataract associated with radiation
35625719	Diabetic cataract of bilateral eyes	443569	Cataract associated with infrared radiation
4109548	Drug-induced cataract	36717554	Cataract and microcornea syndrome
4334130	Elschnig's pearls	375545	Cataract
379811	Hypermature cataract	36715121	Cardiomyopathy with cataract and hip spine disease syndrome
45757567	Hypermature senile cataract	3657086	Bilateral congenital zonular cataract
37208006	Hypermature senile cataract of left eye	37207995	Bilateral congenital posterior subcapsular polar cataracts of eyes
37208004	Hypermature senile cataract of right eye	37207996	Bilateral congenital nuclear cataracts of eyes
40487893	Immature cataract	3657147	Bilateral congenital cortical cataract of eyes

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
4210432	Immature cortical cataract	3657068	Bilateral congenital combined form cataract of eyes
376399	Incipient cataract	36684791	Bilateral congenital cataract of eyes
764826	Incipient cataract of left eye	37310624	Bilateral congenital anterior subcapsular polar cataracts
765724	Incipient cataract of right eye	3657025	Bilateral cataract of eyes due to and following trauma
40482507	Incipient senile cataract	36714335	Autosomal dominant optic atrophy and cataract
4319589	Intumescent cataract	4259620	Anterior capsule opacification following extraction of cataract
4109424	Lamellar zonular cataract	436118	After-cataract with vision obscured following extraction of cataract
37108935	Left after-cataract not obscuring vision	37309694	After-cataract of right eye
4334870	Malnutrition-dehydration cataract	37309693	After-cataract of left eye
377285	Mature cataract	37108936	After-cataract of bilateral eyes
4152554	Mixed type cataract	-	-
4130588	Morgagnian cataract	-	-
372905	Myotonic cataract	-	-
761600	Non age-related cataract of bilateral eyes	-	-
761599	Non age-related cataract of left eye	-	-
765243	Non age-related cataract of right eye	-	-
377274	Nonsenile cataract	-	-
373769	Nuclear cataract	-	-
4230391	Nuclear sclerotic cataract	-	-
439297	Nuclear senile cataract	-	-
4048060	Partial cataract	-	-
4197734	Posterior subcapsular cataract	-	-

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
436976	Posterior subcapsular polar cataract	-	-
765918	Posterior subcapsular polar cataract of bilateral eyes	-	-
761592	Posterior subcapsular polar cataract of left eye	-	-
761593	Posterior subcapsular polar cataract of right eye	-	-
438749	Posterior subcapsular polar senile cataract	-	-
36685057	Posterior subcapsular polar senile cataract of left eye	-	-
36685058	Posterior subcapsular polar senile cataract of right eye	-	-
40479994	Presenile cataract	-	-
36713345	Presenile cataract of bilateral eyes	-	-
37208213	Presenile cataract of left eye	-	-
37208214	Presenile cataract of right eye	-	-
37111464	Punctate age-related cataract	-	-
4230930	Punctate cataract	-	-
37108934	Right after-cataract not obscuring vision	-	-
35624213	Secondary cataract	-	-
761583	Secondary cataract of bilateral eyes with vision obscured	-	-
761586	Secondary cataract of left eye	-	-
761585	Secondary cataract of left eye with vision obscured	-	-
761587	Secondary cataract of right eye	-	-
761584	Secondary cataract of right eye with vision obscured	-	-
381295	Senile cataract	-	-

Concept id included	Concept Name: Included	Concept id excluded	Concept Name: excluded
37208007	Senile combined form cataract of left eye	-	-
37208005	Senile combined form cataract of right eye	-	-
441006	Soemmerring's ring	-	-
4007944	Stationary cataract	-	-
4319588	Subcapsular cataract	-	-
4154554	Suture tip cataract	-	-
381279	Tetanic cataract	-	-
761603	Total cataract of lens of bilateral eyes	-	-
761602	Total cataract of lens of left eye	-	-
761601	Total cataract of lens of right eye	-	-
4109544	Total, mature senile cataract	-	-
374646	Toxic cataract	-	-
4108983	Toxic cataract not due to drugs	-	-
44783427	Zonular nonsenile cataract	-	-

*Congenital, genetic, syndromic forms, post-surgical artifact codes, radiation-induced or traumatic cataract codes were excluded.

Depression

Concept id	Concept Code	Concept Name	Exclude	Descendants
44805550	764711000000106	Single major depressive episode, in remission	Yes	Yes
44813499	764701000000109	Recurrent major depressive episodes, in remission	Yes	Yes
44782943	698957003	Depressive disorder in remission	Yes	Yes
440383	35489007	Depressive disorder	-	Yes

Anxiety

Concept id	Concept Code	Concept Name	Exclude	Descendants
441542	48694002	Anxiety	-	Yes

Haemoptysis

Concept id	Concept Code	Concept Name	Exclude	Descendants
261687	66857006	Hemoptysis	-	Yes
4048152	206304007	Perinatal hemoptysis	Yes	Yes

Preliminary list of concept definitions for pulmonary exacerbation

Pulmonary exacerbation

Concept id	Concept Code	Concept Name	Exclude	Descendants
4193169	312133006	Viral respiratory infection	-	Yes
4181583	54150009	Upper respiratory infection	-	Yes
35624318	766983005	Susceptibility to respiratory infection associated with CD8alpha chain mutation	-	Yes
45768834	707351006	Institution-acquired respiratory infection	-	Yes
4193174	312149008	Fungal respiratory infection	-	Yes
4207184	312117008	Bacterial respiratory infection	-	Yes
44788779	201031000000108	Asthma trigger - respiratory infection	Yes	Yes
4112341	195647007	Acute respiratory infections	-	Yes
3183290	13840001000004105	Pulmonary exacerbation cystic fibrosis	-	Yes

Systemic Antibiotics

Concept id	Concept Code	Concept Name	Exclude*	Descendants
46221507	1603834	avibactam	-	Yes
46274210	1040004	ceftaroline fosamil	-	Yes
45892599	1597609	ceftolozane	-	Yes
45774861	1539239	dalbavancin	-	Yes
45892419	1596450	gentamicin	-	Yes
45776147	1547611	oritavancin	-	Yes
45775686	1540825	tedizolid	-	Yes
43009082	OMOP4700508	cefbuperazone sodium	-	Yes

43009044	OMOP4700470	cefcapene pivoxil hydrochloride hydrate	-	Yes
43008993	OMOP4700419	cefminox sodium	-	Yes
43009045	OMOP4700471	cefpiramide sodium	-	Yes
43009083	OMOP4700509	cefroxadine	-	Yes
43008994	OMOP4700420	ceftezole sodium	-	Yes
43009087	OMOP4700513	flomoxef sodium	-	Yes
43009022	OMOP4700448	isepamicin sulfate	-	Yes
43009067	OMOP4700493	ribostamycin sulfate	-	Yes
43009009	OMOP4700435	sultamicillin	-	Yes
40798709	OMOP2721059	Cefacetrile	-	Yes
40798700	OMOP2721060	Cefazedone	-	Yes
40798704	OMOP2721061	Cefmenoxime	-	Yes
40798981	OMOP2721332	Nifurtoinol	-	Yes
40799027	OMOP2721386	Piromidic Acid	-	Yes
40799118	OMOP2721468	Sulfametoxydiazine	-	Yes
40799120	OMOP2721470	Sulfaperin	-	Yes
40799121	OMOP2721471	Sulfaphenazole	-	Yes
40166675	473837	telavancin	-	Yes
37498010	2265702	cefiderocol	-	Yes
37496518	2198944	lefamulin	-	Yes
36878831	OMOP1007304	nadifloxacin	-	Yes
35884386	OMOP5031290	Rufloxacin	-	Yes
35198192	OMOP4819557	aspoxicillin hydrate	-	Yes
35198093	OMOP4819458	biapenem	-	Yes
35197989	OMOP4819354	carumonam sodium	-	Yes
35197975	OMOP4819340	cefozopran hydrochloride	-	Yes
35198137	OMOP4819502	cefteram pivoxil	-	Yes
35200469	2055906	eravacycline	-	Yes
35198107	OMOP4819472	faropenem sodium hydrate	-	Yes
35197938	OMOP4819303	garenoxacin mesilate hydrate	-	Yes
35200953	2059269	omadacycline	-	Yes
35198003	OMOP4819368	pazufloxacin mesilate	-	Yes
35197897	OMOP4819262	prulifloxacin	-	Yes
35198144	OMOP4819509	rokitamycin	-	Yes
35200881	2059018	sarecycline	-	Yes
35198165	OMOP4819530	sitafloxacin hydrate	-	Yes
35198145	OMOP4819510	tebipenem pivoxil	-	Yes
19123877	626	amdinocillin	-	Yes

19088223	627	amdinocillin pivoxil	-	Yes
19101402	26397	arbekacin	-	Yes
19086759	2236	cephalothin	-	Yes
19086790	2238	cephapirin	-	Yes
19095043	2408	chlortetracycline	-	Yes
19123240	6084	josamycin	-	Yes
19092353	6513	lymecycline	-	Yes
19126622	7069	moxalactam	-	Yes
19129642	7798	oxolinic acid	-	Yes
19088795	33277	phenethicillin	-	Yes
19125201	66958	pristinamycin	-	Yes
19096054	34649	propicillin	-	Yes
19136024	9462	rolitetracycline	-	Yes
19136044	9806	sisomicin	-	Yes
19136210	10114	streptozocin	-	Yes
19136423	10175	sulfalene	-	Yes
19136426	10176	sulfamerazine	-	Yes
19136429	10178	sulfamethazine	-	Yes
19136481	10183	sulfamoxole	-	Yes
19136493	10188	sulfapyridine	-	Yes
19100438	37775	temocillin	-	Yes
19137362	10463	thiamphenicol	-	Yes
19102105	39823	xibornol	-	Yes
19018516	18609	azidocillin	-	Yes
19015123	1266	azlocillin	-	Yes
19018742	19727	brodimoprim	-	Yes
19070174	2178	cefamandole	-	Yes
19070680	2179	cefatrizine	-	Yes
19028241	20482	cefetamet	-	Yes
19072255	2182	cefmetazole	-	Yes
19028286	20485	cefodizime	-	Yes
19072857	2183	cefonicid	-	Yes
19028288	20486	ceforanide	-	Yes
19051271	2188	cefotiam	-	Yes
19001904	27130	cefpirome	-	Yes
19051345	2190	cefsulodin	-	Yes
19052683	2233	cephaloridine	-	Yes
19047240	21264	clofoctol	-	Yes

19047265	21272	clomocycline	-	Yes
19023508	3328	dibekacin	-	Yes
19050750	42322	fleroxacin	-	Yes
19054936	4448	floxacillin	-	Yes
19064329	25112	flumequine	-	Yes
19010400	113608	fusidate	-	Yes
19069006	26797	hetacillin	-	Yes
19008870	29256	mandelic acid	-	Yes
19003644	6812	methacycline	-	Yes
19072054	29629	methampicillin	-	Yes
19007701	6927	mezlocillin	-	Yes
19072122	30005	midecamycin	-	Yes
19009138	6985	miocamycin	-	Yes
19017585	7337	netilmicin	-	Yes
19015464	31901	nitroxoline	-	Yes
19023254	7629	oleandomycin	-	Yes
19024197	7701	ornidazole	-	Yes
19027679	7960	pefloxacin	-	Yes
19010564	113831	pipemidate	-	Yes
19047071	8372	pivampicillin	-	Yes
19036545	35797	rosoxacin	-	Yes
19063874	9478	roxithromycin	-	Yes
19000817	10168	sulbenicillin	-	Yes
19000818	10172	sulfadimethoxine	-	Yes
19000820	10181	sulfamethoxypyridazine	-	Yes
19040624	37328	sulfametrole	-	Yes
19002077	10322	talampicillin	-	Yes
19078399	57021	teicoplanin	-	Yes
19041153	37771	temafloxacin	-	Yes
19006043	10864	troleandomycin	-	Yes
1790868	641	amikacin	-	Yes
1768849	2176	cefaclor	-	Yes
1769535	2177	cefadroxil	-	Yes
1771162	2180	cefazolin	-	Yes
1796458	25037	cefdinir	-	Yes
1748975	20481	cefepime	-	Yes
1796435	25033	cefixime	-	Yes
1773402	2184	cefoperazone	-	Yes

1774470	2186	cefotaxime	-	Yes
1774932	2187	cefotetan	-	Yes
1775741	2189	cefoxitin	-	Yes
1749008	20489	cefpodoxime	-	Yes
1776684	2191	ceftazidime	-	Yes
1749083	20492	ceftibuten	-	Yes
1777254	2192	ceftizoxime	-	Yes
1777806	2193	ceftriaxone	-	Yes
1778162	2194	cefuroxime	-	Yes
1786621	2231	cephalexin	-	Yes
1786842	2239	cephradine	-	Yes
1797513	2551	ciprofloxacin	-	Yes
1750500	21212	clarithromycin	-	Yes
1759842	48203	clavulanate	-	Yes
1800835	2625	cloxacillin	-	Yes
1786617	22299	daptomycin	-	Yes
1790024	23437	dirithromycin	-	Yes
1789276	228476	gatifloxacin	-	Yes
1778262	5690	imipenem	-	Yes
1784749	6099	kanamycin	-	Yes
1790692	6398	lincomycin	-	Yes
1789515	229367	quinupristin	-	Yes

*Topical, ophthalmic, inhalation, vaginal, optic and nasal concept ids were excluded.

ANNEX II. ENCePP checklist study protocol

Study title:
DARWIN EU® - Drug utilisation study in individuals with cystic fibrosis in Europe

EU PAS Register® number: EUPAS1000000708
Study reference number (if applicable): P4-C1-008

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

Comments:

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

Comments:

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

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

Comments:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Dina Vojinovic

Date: 17th June 2025

Signature: