Study Report

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

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Version 4.0

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Public

CONTENTS

<table>
<tr><td>Study title</td><td>DARWIN EU® - Drug utilisation study in individuals with cystic fibrosis in Europe</td></tr>
<tr><td>Protocol version</td><td>V4.0</td></tr>
<tr><td>Date</td><td>29/01/2026</td></tr>
<tr><td>EUPAS number</td><td>EUPAS1000000708</td></tr>
<tr><td>Active substance</td><td>CFTR modulator therapy
<table>
<tr><th>Drug class</th><th>Drug name</th><th>WHO ATC classification code</th></tr>
<tr><td rowspan="4">CFTR modulators</td><td>Ivacaftor</td><td>R07AX02</td></tr>
<tr><td>Ivacaftor and lumacaftor</td><td>R07AX30</td></tr>
<tr><td>Ivacaftor and tezacaftor</td><td>R07AX31</td></tr>
<tr><td>Ivacaftor, tezacaftor, and elexacaftor</td><td>R07AX32</td></tr>
</table>
Supportive CF therapies
<table>
<tr><th>Drug class</th><th>Drug name</th><th>WHO ATC classification code</th></tr>
<tr><td>Bile acid preparations</td><td>Ursodeoxycholic acid</td><td>A05AA02</td></tr>
<tr><td>Pancreatic enzymes</td><td>Multienzymes (lipase, protease etc.)</td><td>A09AA02</td></tr>
<tr><td>Mucolytics</td><td>Dornase alfa (desoxyribonuclease)</td><td>R05CB13</td></tr>
<tr><td>Mucolytics</td><td>Mannitol, acetylcysteine, ambroxol</td><td>R05CB</td></tr>
<tr><td>Selective beta-2-adrenoreceptor agonists</td><td>Salbutamol</td><td>R03AC</td></tr>
<tr><td>Aminoglycoside antibacterials</td><td>Tobramycin</td><td>J01GB01</td></tr>
<tr><td>Proton pump inhibitors</td><td>All ingredients</td><td>A02BC</td></tr>
</table></td></tr>
<tr><td>Medicinal product</td><td>The study includes CFTR modulator therapies authorised for the treatment of cystic fibrosis. A complete list of included medicinal products is provided in Annex I.</td></tr>
<tr><td>Research question and objectives</td><td>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 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</td></tr>
</table>

	by paediatric and adult populations, and time since treatment initiation (one- and two-years post-initiation).
Countries of study	France, Germany, Italy, Norway, Spain, the United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

1. TITLE

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

2. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientists	Gargi Jadhav Akram Mendez 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
CDW Bordeaux	Guillaume Verdy	Centre Hospitalier Universite de Bordeaux
CPRD GOLD	Marta Pineda Moncusí 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 TH Trinh Saeed Hayat	University of Oslo
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. DATA SOURCES

The study was conducted using routinely collected data from 7 data sources in 6 European Countries (4 EU countries, the United Kingdom, and Norway). All data sources were previously mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

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

Detailed information on data sources is described below.

Country	Name of Data source	Type of data	Number of active individuals	Calendar period covered by each data source
France	APHM	EHR, claims, registries	0.25 million	2021 until 11/01/2025
France	CDW Bordeaux	EHR	0.25 million	2005 until 21/08/2025
Germany	IQVIA DA Germany	EHR	4.48 million	1992 until 31/03/2025
Italy	POLIMI	EHR	0.09 million	2006 until 13/05/2025
Norway	NLHR	Registry	6.95 million	2008 until 29/10/2024
Spain	H12O	EHR, registry	0.29 million	2015 until 27/02/2025
The United Kingdom	CPRD GOLD	EHR	2.83 million	1992 until 01/01/2025

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

4. 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 aimed 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 aimed to characterise the use of CFTR modulator therapy in individuals with a CF diagnosis. The study described patient-level treatment patterns, including switching between CFTR modulators (*objective 1*), characterised individuals initiating CFTR modulator treatment (*objective 2*), evaluated patient-level treatment utilisation by assessing treatment duration, cumulative dose, number of repeated prescriptions of CFTR modulator treatment (*objective 3*), and estimated 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 included 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 data source were included. Inclusion criteria required 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 did 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

WHO ATC = World Health Organisation Anatomical Therapeutic Chemical

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. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy
5. Norwegian Linked Health Registry data (NLHR), Norway
6. Hospital Universitario 12 de Octubre (H12O), Spain
7. Clinical Practice Research Datalink GOLD (CPRD GOLD), the United Kingdom

Statistical analysis

Descriptive characterisation was performed at the patient level (*objective 1*). The index date was 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 were described, including the use of treatment combinations. Sunburst and Sankey diagrams were used to visualise treatment patterns and sequences over time. The statistical analysis was performed based on OMOP CDM mapped data using the *TreatmentPatterns* R package.

Patient demographics, including age and sex, were 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 was 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 are presented as numbers and proportions, overall (for any CFTR modulator treatment) and by active ingredient. This analysis was conducted using *CohortCharacteristics* and *DrugUtilisation* R packages based on OMOP CDM mapped data.

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

Incidence rates of pulmonary exacerbation were estimated following CFTR modulator treatment initiation (overall (any CFTR modulator) and by active ingredient level) in individuals with CF (*objective 5*). These results are expressed as the number of individuals with pulmonary exacerbation following CFTR modulator treatment initiation per 1,000 PYs. Incidence rates were 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 were performed based on OMOP CDM mapped data using the *IncidencePrevalence* R package.

Duration of CFTR modulator treatment (overall (any CFTR modulator) and by active ingredient level), cumulative dose, and number of or repeated prescriptions were calculated and summarised, providing the minimum, quartiles, and maximum, where available *(objective 3)*. This analysis was conducted using the *DrugUtilisation* R package based on OMOP CDM mapped data.

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

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

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

Results

A total of 801 individuals with a prescription record for any CFTR modulator therapy during the study period were included across seven European data sources, with the largest contributions from NLHR (34.08%) and IQVIA DA Germany (21.35%). The most frequently used therapies were ivacaftor (n=506),

fixed-dose combination of ivacaftor, tezacaftor, elexacaftor (n=398), and fixed-dose combination of ivacaftor and lumacaftor (n=229). Ivacaftor and tezacaftor combination products were less frequently prescribed (n=43), with 86% of cases reported from IQVIA DA Germany. Ivacaftor prescription records reflected product-level exposure only, as available data did not allow differentiation between monotherapy and ivacaftor prescribed with other CFTR modulators.

Median age at treatment initiation for any CFTR modulator ranged from 16 years in APHM and CDW Bordeaux to 34 years in CPRD GOLD. The highest proportion of paediatric prescriptions was observed in CDW Bordeaux (59.38%) and APHM (52.44%), whereas adult prescriptions predominated in IQVIA DA Germany (91.81%) and CPRD GOLD (92.31%). A higher proportion of females was observed across most data sources, ranging from 52.34% in POLIMI to 64.41% in H12O, except in NLHR, where males accounted for 53.85%. Use of supportive therapies (e.g., mucolytics, salbutamol, pancreatic enzymes) was highest prior to CFTR modulator initiation, declined at CFTR modulator treatment start, and either stabilised or increased post-initiation.

Treatment patterns analyses were performed across IQVIA DA Germany, NLHR, and CPRD GOLD. Treatment episodes were constructed using a 120-day gap to account for potential delays in prescription refills, ensuring robust capture of treatment continuity. The most common first-line CFTR modulator treatment was the combination of ivacaftor together with a fixed-dose combination product of ivacaftor, tezacaftor, and elexacaftor, which together constitute the recommended combination regimen for CF (triple therapy). This treatment pattern was consistently predominant in NLHR (77.87%) and IQVIA DA Germany (75.00%). Other first-line treatments varied by data source, with ivacaftor, combinations of ivacaftor and tezacaftor, or ivacaftor and lumacaftor observed in smaller proportions. Switching between CFTR modulator therapies was infrequent. When switching occurred, most transitions were to the combination of ivacaftor together with a fixed-dose product of ivacaftor, tezacaftor, and elexacaftor. Results from CPRD GOLD were not reported due to low sample sizes and data suppression.

Median exposure durations of any CFTR modulator varied widely, from 4 days in CDW Bordeaux to 366 days in H12O in hospital-based sources to 539 days in the NLHR registry and 679 days in IQVIA DA Germany. Median counts of repeated exposure episodes ranged from 1 in CPRD GOLD to 19 in IQVIA DA Germany. Cumulative dose estimates varied widely across data sources and ingredients.

Pre-specified adverse events, including anxiety, cataract, depression, and haemoptysis, were rare. Most data sources reported no events or fewer than five. The incidence rate during the study period could be estimated for anxiety in the overall study population of NLHR treated with any CFTR modulator, with 13 events over 389 PYs (incidence rate: 33.4 per 1,000 PYs), primarily among adults treated with a fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor. For haemoptysis, CDW Bordeaux reported 5 events over 1 PY.

Incidence rates for pulmonary exacerbations were only reported for data sources with sufficient follow-up time and event counts. The NLHR registry was the sole source with adequate data, reporting an incidence rate of 136.06 per 1,000 PYs in the first year following any CFTR modulator initiation and 288.77 per 1,000 PYs in the second year post initiation based on only six events. Ingredient-specific estimates were available for the fixed-dose ivacaftor, tezacaftor and elexacaftor products in NLHR (148.82 per 1,000 PYs in year one and 128.32 per 1,000 PYs in year two).

Sensitivity analyses excluding censoring at treatment end showed measurable incidence rates of anxiety in NLHR and CDW Bordeaux. Additional haemoptysis events were identified in POLIMI, APHM, and CDW Bordeaux, with incidence rates ranging from 18.74 to 60.41 per 1,000 PYs, primarily in adults.

Discussion

This study provides a descriptive overview of CFTR modulator use, treatment patterns, and selected outcomes across seven European data sources. Triple therapy (ivacaftor, tezacaftor, and elexacaftor) was

the predominant first-line regimen, consistent with current clinical practice. Incidence rates of adverse events were low or could not be estimated in most sources, and pulmonary exacerbation rates were estimable only in the NLHR.

While these findings illustrate the potential of routinely collected healthcare data to inform real-world treatment patterns and outcomes in cystic fibrosis, current limitations in data completeness, follow-up, population coverage, and heterogeneity in available data types (hospital versus outpatient) constrained the ability to draw robust conclusions. Observed trends should therefore be regarded as exploratory rather than confirmatory. Future work should focus on improving data completeness, population coverage, and longitudinal follow-up to enable more comprehensive and reliable assessments.

5. LIST OF ABBREVIATIONS

Acronyms/term	Description
APHM	Assistance Publique – Hôpitaux de Marseille
ATC	Anatomical Therapeutic Chemical
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CDM	Common Data Model
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DQD	Data Quality Dashboard
DUS	Drug Utilisation Study
EEG	Electroencephalogram
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GIT	Gastrointestinal tract
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
N/A	Not applicable
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OT	Other
POLIMI	Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
PPIs	Proton-pump inhibitors
PYs	Person years
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine

Acronyms/term	Description
UDCA	Ursodeoxycholic acid
WHO	World Health Organisation

6. AMENDMENTS AND UPDATES

Number	Date	Section of studyprotocol	Amendment or update	Reason
1	September 2025	Methods, results, discussion	A sensitivity analyses using 60-day and 120-day gap was applied in treatment patterns analyses and drug utilisation.	To better reflect treatment continuity and account for potential delays in prescription refills, multiple gap era definitions were applied to construct treatment episodes. This change minimises artificial fragmentation of treatment episodes.
2	October 2025	Results, discussion	Hospital-based data sources excluded from treatment patterns analyses.	Hospital-based data sources were excluded from treatment pattern analyses because they lack outpatient prescription records, which are essential for accurately capturing longitudinal treatment exposure.

7. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	19th June 2025	19th June 2025
Final Study Protocol	August 2025	29th August 2025
Creation of Analytical code	July/August 2025	July/September 2025
Execution of Analytical Code on the data	September 2025	September/October 2025
Draft Study Report	10th October 2025	10th October 2025
Final Study Report	November 2025	29th January 2026

8. 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 genetic therapies (including mRNA), which are currently in clinical development.[1, 3] CFTR modulators have a well-established benefit profile, with substantial evidence demonstrating reductions in pulmonary exacerbations and improvements in liver function. However, potential adverse events have been reported, including 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.

9. 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 data source were included. Inclusion criteria required 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 did 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 started 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 (did 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 was defined as the earliest of following: 1) end of CFTR modulator treatment (overall/at active ingredient level, where applicable), 2) loss to follow-up, 3) end of data availability, 4) date of death, or 5) end of study period (31st December 2024). For treatment pattern analyses, end of CFTR modulator treatment was not an applicable criterion.
Setting:	Primary care, registry, inpatient, and outpatient specialist care setting using data from 7 data sources: APHM (France), CDW Bordeaux (France), IQVIA DA Germany (Germany), POLIMI (Italy), NLHR (Norway), H120 (Spain), and CPRD GOLD (UK).
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 supportive CF therapies at CFTR modulator treatment initiation and across pre-specified time windows, overall and stratified by paediatric and adult populations. The results are 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 data source were included. Eligible individuals were required to 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 did 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 started 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 (did 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 was 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 were not considered mutually exclusive.
Setting:	Primary care, registry, inpatient, and outpatient specialist care setting using data from 7 data sources: APHM (France), CDW Bordeaux (France), IQVIA DA Germany (Germany), POLIMI (Italy), NLHR (Norway), H120 (Spain), and CPRD GOLD (UK).
Main measure of effect:	Incidence rates of pre-specified adverse events were estimated among individuals initiating CFTR modulator treatment following CF diagnosis. These rates were calculated overall (any CFTR modulator) and by active ingredient level. Results are expressed as the number of individuals with the newly diagnosed adverse event of interest per 1,000 person-years (PYs) of individuals fulfilling the inclusion and exclusion criteria). Incidence rates were reported overall and stratified by paediatric and adult populations and calendar year. Incidence rates of pulmonary exacerbation were assessed among individuals initiating CFTR modulator treatment, overall (any CFTR modulator) and by active ingredient. Incidence rates are

	expressed as the number of individuals with the newly diagnosed pulmonary exacerbation per 1,000 PYs of individuals fulfilling the inclusion and exclusion criteria. These were stratified by paediatric and adult populations, and time since CFTR modulator therapy initiation (one and two years post initiation).

10. RESEARCH METHODS

10.1. Study type and study design

A cohort study was conducted using routinely collected health data from 7 data sources. The study comprises 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).

10.2. Study setting and data sources

The study was conducted using routinely collected data from 7 data sources in 6 European Countries (4 EU countries, the United Kingdom, and Norway). All data sources were previously mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

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

For this study, we have selected 7 data sources that were considered fit for purpose from the data sources 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 data sources had sufficient counts of individuals diagnosed with CF and CFTR modulator therapy.

Information on data sources 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 characterised the data and presented it in a dashboard format that was 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. *CohortDiagnostics* 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 data source, 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 Data source	Justification for Inclusion	Health Care setting	Type of data	Number of active subjects	Last observation period
France	APHM	Data source 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	01/2025
France	CDW Bordeaux	Data source 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	08/2025
Germany	IQVIA DA Germany	Data source 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	03/2025
Italy	POLIMI	Data source 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	05/2025
Norway	NLHR	Data source covers healthcare setting where diagnoses of cystic fibrosis and prescriptions for treatments of interest may be recorded	Registry	Registry	6.95 million	10/2024
Spain	H12O	Data source 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	02/2025
The United Kingdom	CPRD GOLD	Data source 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

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ICU = Intensive Care Unit; 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 hospitalisation—capturing approximately 300,000 stays annually. The data source also captures comprehensive drug prescription and administration data, including UCD drug codes, Anatomical Therapeutic Chemical (ATC) classifications, quantities, and dosages, managed through PHARMA software. Additionally, medical, and paramedical notes, such as hospitalisation reports, radiology,

electroencephalogram (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 data source 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]

IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

IQVIA Disease Analyzer (DA) Germany is a data source of de-identified electronic medical records from specialised and primary general practitioners (GPs) in Germany since 1992.[11] 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 data source that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany data source has been demonstrated to be representative of general and specialised practices throughout Germany.

The data source 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.[12, 13]

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 hospitalisation, outpatient visits, laboratory test, therapies, radiology, anatomic pathology, and a REDCap instance for non-profit studies.

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 harmonised 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.

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.

Clinical Practice Research Datalink GOLD (CPRD GOLD), the 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.[14] The source population 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. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 0.89% in England, 61.13% in Scotland, 26.41% in Wales, and 11.57% in Northern Ireland (January 2025).[14]

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 and sex.[14] 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.[15-17]

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.

10.3. Study period

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

10.4. Follow-up

For objectives (*objectives 1 – 5*), study participants were followed from the date of first recorded CFTR modulator treatment (index date (ID)) after CF diagnosis, among individuals who met 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 (did not hold for children <1 year of age). End of follow-up was defined as earliest of following: 1) end of CFTR modulator treatment (overall/at active ingredient level, where applicable), 2) loss to follow-up, 3) end of data availability, 4) date of death, or 5)

end of study period (31st December 2024). End of CFTR modulator treatment was not an applicable criterion for treatment patterns analysis.

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 names	Time Anchor Description	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, OT = other, n/a = not applicable.

10.5. Study population with inclusion and exclusion criteria

The study population (*objectives 1 – 5)* included 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 data source were included. Eligible individuals were required to 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 did 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 were applied on an event-specific basis. Individuals were excluded from the analysis of a specific adverse event if they had a record of that condition within one year before the index date (*objective 4*). This included:

- 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 medications within 30 days prior to the start of follow-up, were 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 data source history	Study participants were 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, OT = other, n/a = not applicable; [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

10.6. Variables

10.6.1. Exposures

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

- Ivacaftor
- Ivacaftor/lumacaftor
- Ivacaftor/tezacaftor
- Ivacaftor/tezacaftor/elexacaftor

The code list is provided in **ANNEX I: List of concept definitions**.

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

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

10.6.2. Outcomes

For this study, the outcomes of interest were the pre-specified adverse events, including cataract, depression, anxiety, and haemoptysis, and pulmonary exacerbation. The code list is provided in **ANNEX I: List of concept definitions.** Phenotype of pre-specified adverse events was determined following input from EMA.

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

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

Pulmonary exacerbation was 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	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	Final 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, 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 names	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	Final 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	Final 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, OT = other, n/a = not applicable;
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

10.6.3. 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*) included:

- 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 were included in the paediatric cohort, while individuals aged ≥18 years at the time of CFTR modulator initiation were included in the adult cohort.

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

- 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 were assessed at ID, while supportive CF therapies were characterised before the ID, at the ID, and across post-index time windows (e.g., any time prior to the ID, 365 days preceding the ID, at the ID, 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. Final code list provided in **Annex I**	Counts	[-Inf, 0], [-365, 0], 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, OT = other, n/a = not applicable;
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

10.7. Study size

No formal sample size calculation was conducted for this descriptive study, as the aim was 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 approximately up to 100 in APHM, CDW Bordeaux, CPRD GOLD, and H12O to 300 in NLHR.

10.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analytics were performed on a subset of the data sources and on a simulated set of patients, and quality control checks were performed. After all the tests were passed, the final package was released in the version-controlled study repository for execution against all the participating data sources. The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results. The study results of all data sources were checked, after which they were made available to the team, and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

10.9. Statistical methods

10.9.1. Patient privacy protection

Cell suppression was applied as required by data sources to protect individual's privacy. Cell counts <5 were masked.

10.9.2. Main statistical methods

The type of analysis by study type was fixed and 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)

CFTR = Cystic fibrosis transmembrane conductance regulator; DUS = Drug Utilisation Study.

R-packages

We used 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 used *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 were defined as follows: exposure starts at the date of the first prescription after a washout. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications: two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 1**, first row. Additionally, 60 days and 120 days gap era were also considered as part of sensitivity analysis.

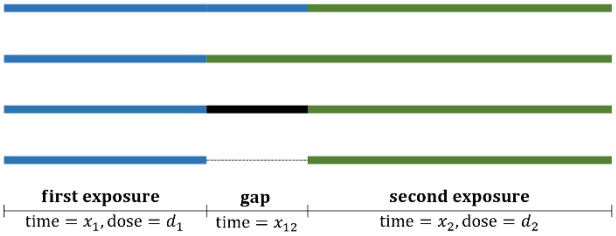
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		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 was considered exposed to the first exposure (**Figure 2**). No time was added at the end of the combined drug era to account for the overlap. If two exposures started at the same date, the overlapping period was considered exposed to both.

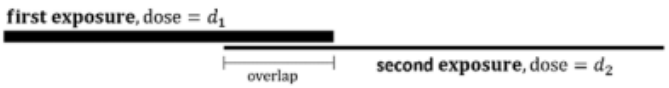
Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 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, were described overall and stratified by paediatric and adult populations (*objective 1*). Additionally, Sunburst plots and Sankey diagrams were used to visualise treatment patterns and sequences over time. Sankey diagrams were censored at end of follow-up as described in section **10.4. Follow-up**.

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

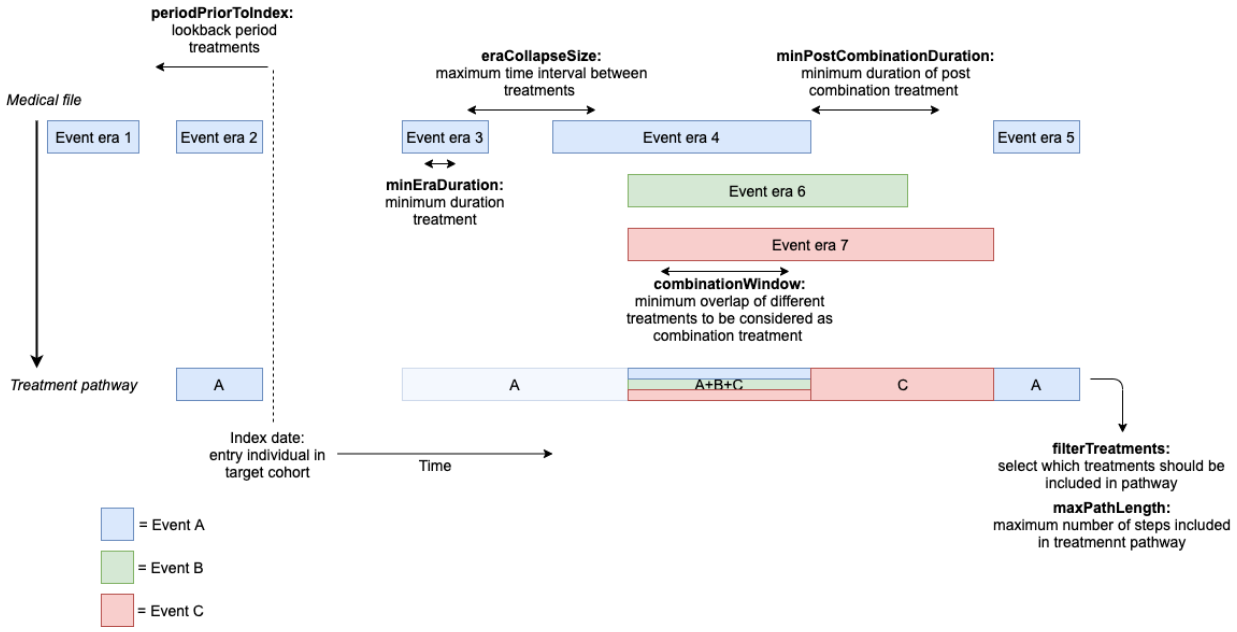


Figure 3. Parameters in *TreatmentPatterns* package.

The 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.

Parameter	Description	Used setting
startAnchor	Reference point for the start date of the analysis.	startDate
windowStart	Number of days offset from the startAnchor to define the start of the observation window.	0
endAnchor	Reference point for the end date of the analysis.	endDate
windowEnd	Number of days offset from the endAnchor to define the end of the observation window.	0
minEraDuration	Minimum duration (in days) that an event era must last to be included in the analysis.	30
splitEventCohorts	Specifies which event cohorts should be split into acute (< X days) and therapy (≥ X days) phases.	NULL
splitTime	Threshold (in days) used to divide event cohorts into acute and therapy phases.	NULL
eraCollapseSize	Time window (in days) within which two eras of the same event cohort are merged into a single era.	30, 60, 120
combinationWindow	Time window (in days) during which two overlapping event cohorts are considered a combination treatment.	30
minPostCombinationDuration	Minimum duration (in days) an event era must last before or after a combination treatment to be included in the analysis.	30
filterTreatments	Selects changes between event cohorts	Changes
maxPathLength	Maximum number of steps allowed in a treatment pathway.	5

Parameter	Description	Used setting
overlapMethod	Method for handling minor overlaps between events. "truncate" shortens the first event to align with the start of the next event.	truncate
concatTargets	Indicates whether multiple target cohorts for the same individual should be merged into a single sequence.	TRUE

For all CFTR modulator treatment initiators following CF diagnosis (*objective 2*), age and sex were assessed at the date of first recorded CFTR modulator prescription (index date) during the study period, overall (any CFTR modulator) and by active ingredient level. Use of other CF related therapies was evaluated in the CFTR modulator treated cohort before the ID, at the ID, and across post-index time windows (any time prior to the ID, 365 days preceding the ID, at the ID, 1 to 30 days, 1 to 90 days, 1 to 365 days, and 1 day to the end of available follow-up). The results are 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) were calculated and summarised, providing the minimum, quartiles, and maximum, where available. The results are presented overall and stratified by paediatric and adult populations. For data sources where duration could not be calculated, due to e.g., missing information on quantity or dosing, treatment duration is not provided.

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

Incidence rates of pre-specified adverse events of special interest were estimated following CFTR modulator treatment initiation in individuals with CF. The pre-specified events of interest were cataract, depression, anxiety, and haemoptysis. These incidence rates are expressed as the number of individuals with the adverse event of interest following CFTR modulator treatment initiation after CF diagnosis per 1,000 PYs of the individuals fulfilling the inclusion and exclusion criteria. Incidence rates were calculated overall and stratified by CFTR modulator active ingredient. Incidence rates are 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 were estimated among individuals initiating CFTR modulator treatment following CF diagnosis, overall and by active ingredient. The results are expressed as the number of individuals with pulmonary exacerbation per 1,000 PYs of the individuals fulfilling the inclusion and exclusion criteria. Incidence rates were 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 were stratified by paediatric and adult populations.

10.9.3. Missing values

We assumed that the absence of a prescription record in the data source means that the person did not receive the respective CFTR modulator treatment. Similarly, for assessment of comorbidities, we assumed 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. These assumptions reflect standard practice in observational research and are necessary for operationalising analyses, however, they rely on the completeness and accuracy of data capture within each data source.

10.9.4. Sensitivity analysis

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

Additionally, a sensitivity analyses was performed using 60-day and 120-day gap era in treatment patterns analyses and drug utilisation *(objectives 1, 3)*. Shorter gap definitions (e.g., 30 days) may artificially fragment treatment episodes, misclassifying ongoing therapy as discontinuation due to potential delay in prescription refills. The longer gap era (e.g., 120-day) was selected to better reflect real-world treatment continuity and to minimise artificial fragmentation.

11. DATA MANAGEMENT

11.1. Data management

All data sources were mapped to the OMOP CDM. This enabled the use of standardised analytics and tools across the network since the structure of the data, and the terminology system was harmonised. The OMOP CDM 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 was written in R. Each data partner executed the study code against their data source containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

11.2. Data storage and protection

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

All data sources used in this study were 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 were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

12. QUALITY CONTROL

General data source quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it was expected that data partners have run the OHDSI *DataQualityDashboard* tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focused on checks that described the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories had one or more subcategories and were evaluated in two contexts: validation and verification. Validation relates to how well data aligned with external benchmarks with expectations derived from known true standards, while verification related to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for medicinal products, a systematic search of possible codes for inclusion was identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this then queried the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, *DrugExposureDiagnostics* was run to assess the use of different codes across the data sources contributing to the study.

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

13. RESULTS

The full set of the results from this study can be assessed through an interactive web application ("Shiny application") at EUPAS1000000708.

13.1. Participants

A total of 801 individuals met all inclusion criteria and were retained in the final study population across seven data sources, based on prescription records for any CFTR modulator product (APHM: 82, CDW Bordeaux: 96, IQVIA DA Germany: 171, POLIMI: 107, NLHR: 273, H12O: 59, CPRD GOLD: 13) (**Table 10**). The largest contributions were from NLHR (34.08%) and IQVIA DA Germany (21.35%).

Treatment exposures were defined using prescription records for individual CFTR modulator products. For ivacaftor, 506 individuals were included in the final study population (APHM: 29, CDW Bordeaux: 18, IQVIA DA Germany: 122, POLIMI: 63, NLHR: 208, H12O: 55, CPRD GOLD: 11), with NLHR (41.11%) and IQVIA DA Germany (24.11%) contributing to the largest proportion of individuals. Ivacaftor prescription records were reflecting product level exposure and did not distinguish between ivacaftor prescribed as monotherapy and ivacaftor dispensed as part of combination CFTR therapies. As a result, individuals may be included in the ivacaftor category even when ivacaftor was not used as stand-alone therapy.

For the fixed-dose ivacaftor and lumacaftor combination products, 229 individuals were retained (APHM: 48, CDW Bordeaux: 53, IQVIA DA Germany: 41, POLIMI: 40, NLHR: 47), with hospital-based data sources CDW Bordeaux (23.14%) and APHM (20.96%), and NLHR (20.52%) contributing to the largest proportion of individuals. CPRD GOLD reported counts below 5, and H12O reported none for this therapy.

For the fixed-dose combination of ivacaftor and tezacaftor, 43 individuals were included, primarily from IQVIA DA Germany (n=37; 86.05%) and CPRD GOLD (n=6; 13.95%). Suppressed counts (<5) were reported in CDW Bordeaux and NLHR, and no individuals were retained from APHM, POLIMI, or H12O.

Finally, for the fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor products, 398 individuals met all inclusion criteria (APHM: 31, CDW Bordeaux: 28, IQVIA DA Germany: 84, POLIMI: 20, NLHR: 198, H12O: 37), with NLHR (49.75%) and IQVIA DA Germany (21.11%) contributing the most.

Table 10. Attrition table for study population (new CFTR modulator user cohort).

CFTR modulator therapy	Variable	APHM (n)	CDW Bordeaux (n)	IQVIA DA Germany (n)	POLIMI (n)	NLHR (n)	H12O (n)	CPRD GOLD (n)
Any CFTR modulator	Initial qualifying events	95	110	266	127	278	70	15
	Possible 180 days follow up	91	101	258	119	278	65	15
	Sufficient Prior Observation	82	96	171	107	273	59	13
	Follow-up censored at death	82	96	171	107	273	59	13
Ivacaftor	Initial qualifying events	37	26	192	76	213	66	13
	Possible 180 days follow up	33	19	186	68	213	61	13
	Sufficient Prior Observation	29	18	122	63	208	55	11
	Follow-up censored at death	29	18	122	63	208	55	11
Ivacaftor and lumacaftor*	Initial qualifying events	52	56	55	47	47	0	<5
	Possible 180 days follow up	52	56	55	47	47	0	<5
	Sufficient Prior Observation	48	53	41	40	47	0	<5
	Follow-up censored at death	48	53	41	40	47	0	<5
Ivacaftor and tezacaftor*	Initial qualifying events	0	<5	57	0	<5	0	7
	Possible 180 days follow up	0	<5	57	0	<5	0	7
	Sufficient Prior Observation	0	<5	37	0	<5	0	6
	Follow-up censored at death	0	<5	37	0	<5	0	6
Ivacaftor, tezacaftor, and elexacaftor*	Initial qualifying events	40	31	134	24	203	46	0
	Possible 180 days follow up	36	30	126	20	203	41	0
	Sufficient Prior Observation	31	28	84	20	198	37	0
	Follow-up censored at death	31	28	84	20	198	37	0

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, n = number of subjects.
*Fixed-dose combination CFTR modulator products.

13.2. Patient-level characterisation of CFTR modulator users

13.2.1. Demographic characteristics for any CFTR modulator therapy

The median age at the first record of any CFTR modulator prescription during the study period varied across data sources, ranging from 16 years in APHM and CDW Bordeaux to 34 years in CPRD GOLD (**Table 11**). The age distribution showed notable variations, with the highest proportion of paediatric prescriptions (<18 years) observed in CDW Bordeaux (59.38%) and APHM (52.44%). In contrast, adult prescriptions (≥18 years) were predominant in all other data sources, with the highest frequencies in IQVIA DA Germany (91.81%) and CPRD GOLD (92.31%). The age range extended from as young as 1 year in APHM and NLHR to 82 years in NLHR.

Sex distribution was generally skewed towards females across most of the hospital-based and primary care data sources, with proportions ranging from 52.34% in POLIMI to 64.41% in H12O. NLHR registry was the only data source where males accounted for a slightly larger proportion (53.85%), while APHM reported a balanced distribution (50.00% female, 50.00% male) (**Table 11**).

Descriptive characteristics stratified by paediatric and adult populations are presented in **Table S1** in **ANNEX II.**

Table 11. Characteristics of individuals diagnosed with CF at the time of first recorded prescription of any CFTR modulator treatment during the study period (2015–2024), presented for the overall population and by data source.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Number of subjects	82	96	171	107	273	59	13
Age (years), median [q25–q75]	16 [11–29]	16 [11–23]	33 [25–40]	29 [18–37]	25 [14–39]	30 [19–36]	34 [28–41]
Age (years), range (min–max)	1–67	2–48	2–62	2–55	1–82	3–72	9–60
Age group, n (%)							
• <18 years	43 (52.44%)	57 (59.38%)	14 (8.19%)	23 (21.50%)	97 (35.53%)	11 (18.64%)	<5
• ≥18 years	39 (47.56%)	39 (40.63%)	157 (91.81%)	84 (78.50%)	176 (64.47%)	48 (81.36%)	12 (92.31%)
Sex, n (%)							
• Females	41 (50.00%)	54 (56.25%)	99 (57.89%)	56 (52.34%)	126 (46.15%)	38 (64.41%)	7 (53.85%)
• Males	41 (50.00%)	42 (43.75%)	72 (42.11%)	51 (47.66%)	147 (53.85%)	21 (35.59%)	6 (46.15%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD.
n = number of subjects, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

13.2.2. Demographic characteristics by CFTR modulator

Demographic characterisation of individuals initiating CFTR modulator therapy revealed distinct patterns across CFTR modulators and data sources (**Table 12**). Initial ivacaftor prescriptions during study period were recorded at median ages ranging from 17 years (APHM) to 35 years (IQVIA DA Germany), with an overall age range of 2 to 82 years. Paediatric prescriptions of ivacaftor were most frequently recorded in APHM (51.72%), while adult prescriptions predominated in other data sources, ranging from 66.67% in CDW Bordeaux to 94.26% in IQVIA DA Germany. Sex distribution was either balanced or female-predominant across most contributing data sources, except in NLHR where males were more prevalent (**Table 12**).

For the fixed-dose combination of ivacaftor and lumacaftor, median age at first prescription during the study period ranged from 13 years in CDW Bordeaux to 32 years in IQVIA DA Germany, with an age range between 1 and 59 years. Paediatric prescriptions were most prominent in CDW Bordeaux (64.15%), APHM (58.33%), and NLHR (53.19%), whereas adult prescriptions predominated in IQVIA DA Germany (85.37%) and POLIMI (72.50%). Sex distribution varied across data sources without a consistent pattern.

Fixed-dose ivacaftor and tezacaftor combination product prescriptions were observed exclusively in adult populations, with median ages between 30 (CPRD GOLD) and 37 (IQVIA DA Germany) years and an observed age range of 20 to 62 years. Sex distribution showed a female predominance.

For the fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor, median ages at initial prescription ranged from 14 years in CDW Bordeaux to 33 years in IQVIA DA Germany, with an overall age range of 2 to 82 years. Paediatric prescriptions were most frequent in CDW Bordeaux (67.86%), while adult prescriptions predominated in other data sources including APHM (58.06%), IQVIA DA Germany (92.86%), POLIMI (90.00%), NLHR (66.16%), and H12O (81.80%).

Descriptive characteristics stratified by paediatric and adult populations are presented in **Table S2-Table S5** in **ANNEX II.**

Table 12. Characteristics of individuals diagnosed with CF at the time of first recorded prescription of CFTR modulator treatment during study period (2015–2024), stratified by active ingredient and data source.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Ivacaftor							
Number of subjects	29	18	122	63	208	55	11
Age (years), median [q25–q75]	17 [10–34]	21 [16–26]	35 [27–42]	31 [22–41]	30 [15–41]	30 [19–36]	32 [26–40]
Age (years), range (min–max)	4–67	9–38	8–62	2–55	6–82	3–72	9–60
Age group, n (%)							
• <18 years	15 (51.72%)	6 (33.33%)	7 (5.74%)	12 (19.05%)	65 (31.25%)	10 (18.18%)	<5
• >= 18 years	14 (48.28%)	12 (66.67%)	115 (94.26%)	51 (80.95%)	143 (68.75%)	45 (81.82%)	10 (90.91%)
Sex, n (%)							
• Female	15 (51.72%)	10 (55.56%)	68 (55.74%)	38 (60.32%)	93 (44.71%)	36 (65.45%)	6 (54.55%)
• Male	14 (48.28%)	8 (44.44%)	54 (44.26%)	25 (39.68%)	115 (55.29%)	19 (34.55%)	5 (45.45%)
Ivacaftor and lumacaftor							
Number of subjects	48	53	41	40	47	NA	<5
Age (years), median [q25–q75]	16 [11–25]	13 [11–21]	32 [23–38]	24 [16–30]	17 [12–23]	NA	NA
Age (years), range (min–max)	1–59	2–48	2–49	11–45	1–44	NA	NA
Age group, n (%)							
• < 18 years	28 (58.33%)	34 (64.15%)	6 (14.63%)	11 (27.50%)	25 (53.19%)	NA	NA
• >= 18 years	20 (41.67%)	19 (35.85%)	35 (85.37%)	29 (72.50%)	22 (46.81%)	NA	NA
Sex, n (%)							
• Female	23 (47.92%)	32 (60.38%)	25 (60.98%)	17 (42.50%)	19 (40.43%)	NA	NA
• Male	25 (52.08%)	21 (39.62%)	16 (39.02%)	23 (57.50%)	28 (59.57%)	NA	NA
Ivacaftor and tezacaftor							

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Number of subjects	NA	<5	37	NA	<5	NA	6
Age (years), median [q25–q75]	NA	NA	37 [28–43]	NA	NA	NA	30 [25–36]
Age (years), range (min–max)	NA	NA	20–62	NA	NA	NA	22–56
Age group, n (%)							
• < 18 years	NA	<5	NA	NA	<5	NA	NA
• >= 18 years	NA	<5	37 (100.00%)	NA	<5	NA	6 (100.00%)
Sex, n (%)							
• Female	NA	<5	23 (62.16%)	NA	<5	NA	<5
• Male	NA	<5	14 (37.84%)	NA	<5	NA	<5
Ivacaftor, tezacaftor, and elexacaftor							
Number of subjects	31	28	84	20	198	37	NA
Age (years), median [q25–q75]	29 [11–35]	14 [12–21]	33 [25–40]	31 [22–42]	28 [14–40]	30 [20–36]	NA
Age (years), range (min–max)	4–67	2–47	8–62	10–55	6–82	12–72	NA
Age group, n (%)							
• < 18 years	13 (41.94%)	19 (67.86%)	6 (7.14%)	<5	67 (33.84%)	7 (18.92%)	NA
• >= 18 years	18 (58.06%)	9 (32.14%)	78 (92.86%)	18 (90.00%)	131 (66.16%)	30 (81.08%)	NA
Sex, n (%)							
• Female	17 (54.84%)	13 (46.43%)	46 (54.76%)	9 (45.00%)	93 (46.97%)	23 (62.16%)	NA
• Male	14 (45.16%)	15 (53.57%)	38 (45.24%)	11 (55.00%)	105 (53.03%)	14 (37.84%)	NA

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable.
n = number of subjects, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

13.2.3. Supportive CF therapy use over time

Supportive treatment use in individuals on CFTR modulator therapy (any CFTR modulator) demonstrated consistent temporal patterns across drug classes and data sources (**Table 13**). The therapies assessed included proton pump inhibitors, mucolytics, selective beta-2-adrenoreceptor agonists (salbutamol), bile acid preparations (ursodeoxycholic acid), aminoglycoside antibacterials (tobramycin), and multienzymes (pancreatic enzymes).

Across most therapies, the highest proportions of use occurred before CFTR modulator initiation, particularly in the unrestricted pre-index window and the one-year prior to initiation. At the index date (first recorded CFTR modulator treatment during the study period), a decline in supportive therapy use was consistently observed across data sources and drug classes. In the post-initiation period, therapy use either stabilised or gradually increased, with the highest proportions typically observed in the long-term follow-up window (any time post-index). For example, use of salbutamol showed a rebound in several data sources, indicating continued or resumed need for airway clearance.

Supportive therapy use among paediatric CFTR modulator users (any CFTR modulator) followed consistent temporal patterns across drug classes and data sources (**Table 14**). Mucolytics and salbutamol were the most frequently used therapies prior to CFTR modulator initiation, with high pre-initiation use in CDW Bordeaux, NLHR, and POLIMI. Use of these therapies declined at the index date but remained substantial in the post-initiation period.

Pancreatic enzyme therapy showed in general persistently high use among the paediatric population across various time windows, particularly in NLHR, POLIMI and H12O. Pre-initiation use of proton pump inhibitors was higher in H12O and APHM, while tobramycin showed higher pre-initiation rates in H12O and CDW Bordeaux. Post-initiation persistence for both treatments varied across data sources. Ursodeoxycholic acid use was generally stable across time windows.

In adults on CFTR modulator therapy (any CFTR modulator), supportive treatment use showed consistent temporal patterns across drug classes and data sources (**Table 15**). Proton pump inhibitors, mucolytics, and salbutamol were commonly used prior to initiation, with the highest proportions observed in the unrestricted and one-year pre-index windows. Use declined at the index date, followed by either stabilisation or gradual increases during the post-initiation period. Pancreatic enzymes showed consistently high use across all time windows, with minimal change after initiation in most of the data sources. Bile acid preparations (usodeoxycholic acid) and aminoglycoside antibacterials (tobramycin) demonstrated pre-initiation use, decline at initiation, and gradual increase post-initiation, though absolute proportions varied widely by source.

Similar patterns of supportive therapy use were observed across active ingredient-specific cohorts, both overall and within paediatric and adult populations (**Table S6–Table S17** in **ANNEX II**).

Table 13. Frequency of supportive CF therapies use in individuals on CFTR modulator therapy (any CFTR modulator, plain or fixed-dose combination) across different pre- and post-index windows, in the overall population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	52 (63.41%)	38 (46.34%)	32 (39.02%)	7 (8.54%)	10 (12.20%)	21 (25.61%)	29 (35.37%)
CDW Bordeaux	n (%)	38 (39.58%)	22 (22.92%)	17 (17.71%)	21 (21.88%)	21 (21.88%)	27 (28.12%)	32 (33.33%)
IQVIA DA Germany	n (%)	53 (30.99%)	35 (20.47%)	7 (4.09%)	<5	16 (9.36%)	29 (16.96%)	61 (35.67%)
POLIMI	n (%)	73 (68.22%)	64 (59.81%)	57 (53.27%)	63 (58.88%)	63 (58.88%)	65 (60.75%)	67 (62.62%)
NLHR	n (%)	97 (35.53%)	65 (23.81%)	5 (1.83%)	17 (6.23%)	41 (15.02%)	63 (23.08%)	77 (28.21%)
H12O	n (%)	41 (69.49%)	25 (42.37%)	10 (16.95%)	<5	7 (11.86%)	15 (25.42%)	23 (38.98%)
CPRD GOLD	n (%)	6 (46.15%)	<5	0	<5	<5	<5	6 (46.15%)
Mucolytics								
APHM	N (%)	8 (9.76%)	0	0	0	0	<5	6 (7.32%)
CDW Bordeaux	N (%)	72 (75.00%)	40 (41.67%)	22 (22.92%)	56 (58.33%)	58 (60.42%)	61 (63.54%)	64 (66.67%)
IQVIA DA Germany	N (%)	94 (54.97%)	51 (29.82%)	12 (7.02%)	13 (7.60%)	34 (19.88%)	52 (30.41%)	72 (42.11%)
POLIMI	N (%)	56 (52.34%)	45 (42.06%)	42 (39.25%)	42 (39.25%)	42 (39.25%)	43 (40.19%)	47 (43.93%)
NLHR	N (%)	199 (72.89%)	167 (61.17%)	19 (6.96%)	56 (20.51%)	109 (39.93%)	159 (58.24%)	172 (63.00%)
H12O	N (%)	26 (44.07%)	14 (23.73%)	10 (16.95%)	<5	<5	6 (10.17%)	10 (16.95%)
CPRD GOLD	N (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	N (%)	59 (71.95%)	48 (58.54%)	38 (46.34%)	16 (19.51%)	19 (23.17%)	25 (30.49%)	36 (43.90%)
CDW Bordeaux	N (%)	57 (59.38%)	27 (28.12%)	13 (13.54%)	17 (17.71%)	21 (21.88%)	32 (33.33%)	43 (44.79%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	N (%)	85 (49.71%)	60 (35.09%)	8 (4.68%)	<5	29 (16.96%)	60 (35.09%)	85 (49.71%)
POLIMI	N (%)	60 (56.07%)	49 (45.79%)	36 (33.64%)	37 (34.58%)	37 (34.58%)	37 (34.58%)	41 (38.32%)
NLHR	N (%)	193 (70.70%)	150 (54.95%)	11 (4.03%)	34 (12.45%)	82 (30.04%)	138 (50.55%)	147 (53.85%)
H12O	N (%)	37 (62.71%)	25 (42.37%)	18 (30.51%)	8 (13.56%)	11 (18.64%)	17 (28.81%)	23 (38.98%)
CPRD GOLD	N (%)	11 (84.62%)	9 (69.23%)	0	<5	8 (61.54%)	11 (84.62%)	12 (92.31%)
Bile acid preparations (usodeoxycholic acid)								
APHM	N (%)	34 (43.59%)	28 (35.90%)	20 (25.64%)	<5	5 (6.41%)	14 (17.95%)	22 (28.21%)
CDW Bordeaux	N (%)	15 (16.67%)	13 (14.44%)	13 (14.44%)	14 (15.56%)	14 (15.56%)	16 (17.78%)	16 (17.78%)
IQVIA DA Germany	N (%)	80 (48.78%)	51 (31.10%)	7 (4.27%)	9 (5.49%)	37 (22.56%)	67 (40.85%)	90 (54.88%)
POLIMI	N (%)	45 (42.06%)	45 (42.06%)	42 (39.25%)	43 (40.19%)	43 (40.19%)	44 (41.12%)	46 (42.99%)
NLHR	N (%)	24 (8.86%)	19 (7.01%)	-	<5	11 (4.06%)	18 (6.64%)	20 (7.38%)
H12O	N (%)	21 (38.89%)	11 (20.37%)	<5	<5	5 (9.26%)	7 (12.96%)	8 (14.81%)
CPRD GOLD	N (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	N (%)	35 (42.68%)	12 (14.63%)	6 (7.32%)	7 (8.54%)	8 (9.76%)	12 (14.63%)	16 (19.51%)
CDW Bordeaux	N (%)	67 (69.79%)	34 (35.42%)	15 (15.62%)	21 (21.88%)	25 (26.04%)	30 (31.25%)	36 (37.50%)
IQVIA DA Germany	N (%)	78 (45.61%)	35 (20.47%)	9 (5.26%)	5 (2.92%)	16 (9.36%)	31 (18.13%)	50 (29.24%)
POLIMI	N (%)	54 (50.47%)	39 (36.45%)	29 (27.10%)	32 (29.91%)	34 (31.78%)	34 (31.78%)	36 (33.64%)
NLHR	N (%)	76 (27.84%)	41 (15.02%)	0	5 (1.83%)	17 (6.23%)	34 (12.45%)	41 (15.02%)
H12O	N (%)	42 (71.19%)	27 (45.76%)	16 (27.12%)	14 (23.73%)	19 (32.20%)	25 (42.37%)	26 (44.07%)
CPRD GOLD	N (%)	<5	<5	0	0	<5	<5	<5
Multienzymes (pancreatic enzymes)								

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
POLIMI	N (%)	88 (82.24%)	88 (82.24%)	74 (69.16%)	70 (65.42%)	74 (69.16%)	78 (72.90%)	81 (75.70%)
NLHR	N (%)	175 (64.58%)	162 (59.78%)	21 (7.75%)	77 (28.41%)	144 (53.14%)	177 (65.31%)	189 (69.74%)
H12O	N (%)	47 (87.04%)	29 (53.70%)	15 (27.78%)	<5	13 (24.07%)	23 (42.59%)	29 (53.70%)
CPRD GOLD	N (%)	12 (92.31%)	11 (84.62%)	<5	5 (38.46%)	11 (84.62%)	12 (92.31%)	12 (92.31%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table 14. Frequency of supportive CF therapies use in individuals on CFTR modulator therapy (any CFTR modulator, plain or fixed-dose combination product) across different pre- and post-index windows, in paediatric population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	24 (55.81%)	18 (41.86%)	13 (30.23%)	<5	<5	8 (18.60%)	12 (27.91%)
CDW Bordeaux	n (%)	22 (38.60%)	14 (24.56%)	9 (15.79%)	10 (17.54%)	10 (17.54%)	15 (26.32%)	18 (31.58%)
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5
POLIMI	n (%)	10 (43.48%)	10 (43.48%)	7 (30.43%)	7 (30.43%)	7 (30.43%)	7 (30.43%)	7 (30.43%)
NLHR	n (%)	31 (31.96%)	17 (17.53%)	<5	7 (7.22%)	12 (12.37%)	18 (18.56%)	21 (21.65%)
H12O	n (%)	7 (63.64%)	6 (54.55%)	5 (45.45%)	0	<5	<5	<5
CPRD GOLD	n (%)	<5	0	0	0	0	0	0
Mucolytics								
APHM	n (%)	6 (13.95%)	0	0	0	0	<5	<5
CDW Bordeaux	n (%)	48 (84.21%)	29 (50.88%)	16 (28.07%)	37 (64.91%)	38 (66.67%)	41 (71.93%)	42 (73.68%)
IQVIA DA Germany	n (%)	5 (35.71%)	<5	0	<5	<5	5 (35.71%)	5 (35.71%)
POLIMI	n (%)	17 (73.91%)	15 (65.22%)	15 (65.22%)	15 (65.22%)	15 (65.22%)	15 (65.22%)	16 (69.57%)
NLHR	n (%)	79 (81.44%)	74 (76.29%)	7 (7.22%)	25 (25.77%)	53 (54.64%)	67 (69.07%)	73 (75.26%)
H12O	n (%)	7 (63.64%)	6 (54.55%)	5 (45.45%)	<5	<5	<5	5 (45.45%)
CPRD GOLD	n (%)	0	0	0	0	0	0	0
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	34 (79.07%)	28 (65.12%)	24 (55.81%)	13 (30.23%)	15 (34.88%)	17 (39.53%)	24 (55.81%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CDW Bordeaux	n (%)	39 (68.42%)	18 (31.58%)	5 (8.77%)	7 (12.28%)	10 (17.54%)	21 (36.84%)	29 (50.88%)
IQVIA DA Germany	n (%)	9 (64.29%)	7 (50.00%)	0	0	<5	5 (35.71%)	6 (42.86%)
POLIMI	n (%)	22 (95.65%)	22 (95.65%)	18 (78.26%)	17 (73.91%)	17 (73.91%)	17 (73.91%)	17 (73.91%)
NLHR	n (%)	62 (63.92%)	41 (42.27%)	<5	6 (6.19%)	20 (20.62%)	34 (35.05%)	36 (37.11%)
H12O	n (%)	11 (100.00%)	9 (81.82%)	5 (45.45%)	6 (54.55%)	8 (72.73%)	8 (72.73%)	9 (81.82%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	13 (31.71%)	8 (19.51%)	5 (12.20%)	0	0	<5	7 (17.07%)
CDW Bordeaux	n (%)	10 (18.18%)	8 (14.55%)	8 (14.55%)	9 (16.36%)	9 (16.36%)	10 (18.18%)	10 (18.18%)
IQVIA DA Germany	n (%)	7 (50.00%)	6 (42.86%)	0	<5	5 (35.71%)	6 (42.86%)	8 (57.14%)
POLIMI	n (%)	6 (26.09%)	6 (26.09%)	5 (21.74%)	6 (26.09%)	6 (26.09%)	6 (26.09%)	6 (26.09%)
NLHR	n (%)	14 (14.43%)	12 (12.37%)	-	<5	7 (7.22%)	11 (11.34%)	12 (12.37%)
H12O	n (%)	<5	<5	<5	0	<5	<5	<5
CPRD GOLD	n (%)	0	0	-	0	0	0	0
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	18 (41.86%)	5 (11.63%)	<5	<5	<5	<5	6 (13.95%)
CDW Bordeaux	n (%)	43 (75.44%)	23 (40.35%)	9 (15.79%)	11 (19.30%)	14 (24.56%)	17 (29.82%)	23 (40.35%)
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5
POLIMI	n (%)	12 (52.17%)	9 (39.13%)	7 (30.43%)	7 (30.43%)	8 (34.78%)	8 (34.78%)	8 (34.78%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
NLHR	n (%)	34 (35.05%)	13 (13.40%)	0	<5	6 (6.19%)	9 (9.28%)	14 (14.43%)
H12O	n (%)	8 (72.73%)	5 (45.45%)	5 (45.45%)	5 (45.45%)	5 (45.45%)	5 (45.45%)	5 (45.45%)
CPRD GOLD	n (%)	0	0	0	0	0	0	0
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	21 (91.30%)	21 (91.30%)	14 (60.87%)	13 (56.52%)	14 (60.87%)	14 (60.87%)	16 (69.57%)
NLHR	n (%)	75 (77.32%)	74 (76.29%)	9 (9.28%)	32 (32.99%)	68 (70.10%)	81 (83.51%)	84 (86.60%)
H12O	n (%)	9 (81.82%)	9 (81.82%)	9 (81.82%)	<5	<5	<5	6 (54.55%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table 15. Frequency of supportive CF therapies use in individuals on CFTR modulator therapy (any CFTR modulator, plain or fixed-dose combination) across different pre- and post-index windows, in adult population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	28 (71.79%)	20 (51.28%)	19 (48.72%)	5 (12.82%)	6 (15.38%)	13 (33.33%)	17 (43.59%)
CDW Bordeaux	n (%)	16 (41.03%)	8 (20.51%)	8 (20.51%)	11 (28.21%)	11 (28.21%)	12 (30.77%)	14 (35.90%)
IQVIA DA Germany	n (%)	52 (33.12%)	34 (21.66%)	7 (4.46%)	<5	16 (10.19%)	28 (17.83%)	58 (36.94%)
POLIMI	n (%)	63 (75.00%)	54 (64.29%)	50 (59.52%)	56 (66.67%)	56 (66.67%)	58 (69.05%)	60 (71.43%)
NLHR	n (%)	66 (37.50%)	48 (27.27%)	<5	10 (5.68%)	29 (16.48%)	45 (25.57%)	56 (31.82%)
H12O	n (%)	34 (70.83%)	19 (39.58%)	5 (10.42%)	<5	6 (12.50%)	13 (27.08%)	19 (39.58%)
CPRD GOLD	n (%)	5 (41.67%)	<5	0	<5	<5	<5	6 (50.00%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	<5	<5
CDW Bordeaux	n (%)	24 (61.54%)	11 (28.21%)	6 (15.38%)	19 (48.72%)	20 (51.28%)	20 (51.28%)	22 (56.41%)
IQVIA DA Germany	n (%)	89 (56.69%)	48 (30.57%)	12 (7.64%)	11 (7.01%)	31 (19.75%)	47 (29.94%)	67 (42.68%)
POLIMI	n (%)	39 (46.43%)	30 (35.71%)	27 (32.14%)	27 (32.14%)	27 (32.14%)	28 (33.33%)	31 (36.90%)
NLHR	n (%)	120 (68.18%)	93 (52.84%)	12 (6.82%)	31 (17.61%)	56 (31.82%)	92 (52.27%)	99 (56.25%)
H12O	n (%)	19 (39.58%)	8 (16.67%)	5 (10.42%)	0	0	<5	5 (10.42%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	25 (64.10%)	20 (51.28%)	14 (35.90%)	<5	<5	8 (20.51%)	12 (30.77%)
CDW Bordeaux	n (%)	18 (46.15%)	9 (23.08%)	8 (20.51%)	10 (25.64%)	11 (28.21%)	11 (28.21%)	14 (35.90%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	76 (48.41%)	53 (33.76%)	8 (5.10%)	<5	26 (16.56%)	55 (35.03%)	79 (50.32%)
POLIMI	n (%)	38 (45.24%)	27 (32.14%)	18 (21.43%)	20 (23.81%)	20 (23.81%)	20 (23.81%)	24 (28.57%)
NLHR	n (%)	131 (74.43%)	109 (61.93%)	9 (5.11%)	28 (15.91%)	62 (35.23%)	104 (59.09%)	111 (63.07%)
H12O	n (%)	26 (54.17%)	16 (33.33%)	13 (27.08%)	<5	<5	9 (18.75%)	14 (29.17%)
CPRD GOLD	n (%)	10 (83.33%)	8 (66.67%)	0	<5	7 (58.33%)	10 (83.33%)	11 (91.67%)
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	21 (56.76%)	20 (54.05%)	15 (40.54%)	<5	5 (13.51%)	11 (29.73%)	15 (40.54%)
CDW Bordeaux	n (%)	5 (14.29%)	5 (14.29%)	5 (14.29%)	5 (14.29%)	5 (14.29%)	6 (17.14%)	6 (17.14%)
IQVIA DA Germany	n (%)	73 (48.67%)	45 (30.00%)	7 (4.67%)	8 (5.33%)	32 (21.33%)	61 (40.67%)	82 (54.67%)
POLIMI	n (%)	39 (46.43%)	39 (46.43%)	37 (44.05%)	37 (44.05%)	37 (44.05%)	38 (45.24%)	40 (47.62%)
NLHR	n (%)	10 (5.75%)	7 (4.02%)	-	<5	<5	7 (4.02%)	8 (4.60%)
H12O	n (%)	18 (41.86%)	8 (18.60%)	<5	<5	<5	5 (11.63%)	6 (13.95%)
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	17 (43.59%)	7 (17.95%)	<5	5 (12.82%)	5 (12.82%)	9 (23.08%)	10 (25.64%)
CDW Bordeaux	n (%)	24 (61.54%)	11 (28.21%)	6 (15.38%)	10 (25.64%)	11 (28.21%)	13 (33.33%)	13 (33.33%)
IQVIA DA Germany	n (%)	77 (49.04%)	34 (21.66%)	9 (5.73%)	5 (3.18%)	16 (10.19%)	30 (19.11%)	49 (31.21%)
POLIMI	n (%)	42 (50.00%)	30 (35.71%)	22 (26.19%)	25 (29.76%)	26 (30.95%)	26 (30.95%)	28 (33.33%)
NLHR	n (%)	42 (23.86%)	28 (15.91%)	0	<5	11 (6.25%)	25 (14.20%)	27 (15.34%)
H12O	n (%)	34 (70.83%)	22 (45.83%)	11 (22.92%)	9 (18.75%)	14 (29.17%)	20 (41.67%)	21 (43.75%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	<5	0	0	<5	<5	<5
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	67 (79.76%)	67 (79.76%)	60 (71.43%)	57 (67.86%)	60 (71.43%)	64 (76.19%)	65 (77.38%)
NLHR	n (%)	100 (57.47%)	88 (50.57%)	12 (6.90%)	45 (25.86%)	76 (43.68%)	96 (55.17%)	105 (60.34%)
H12O	n (%)	38 (88.37%)	20 (46.51%)	6 (13.95%)	<5	10 (23.26%)	19 (44.19%)	23 (53.49%)
CPRD GOLD	n (%)	11 (91.67%)	10 (83.33%)	<5	<5	10 (83.33%)	11 (91.67%)	11 (91.67%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

13.3. Treatment patterns

Note: Treatment patterns were evaluated using multiple gap era definitions (30, 60, and 120 days) to construct treatment episodes. Considering the characteristics of cystic fibrosis treatment and potential delays in prescription refills, the results are presented using a 120-day gap era, which more accurately reflects treatment continuity and minimises artificial fragmentation. Results based on shorter gap eras (30 and 60 days) are available in the Shiny application (EUPAS1000000708) for reference. Hospital-based data sources were excluded from treatment pattern analyses because they generally lack outpatient prescription records, which are essential for accurately capturing longitudinal treatment exposure. This means that treatment patterns were assessed in IQVIA DA Germany, NLHR, and CPRD GOLD.

The most frequently observed first-line treatment among individuals diagnosed with cystic fibrosis and initiating CFTR modulator therapy was the combination of ivacaftor together with a fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor, which together constitute the recommended combination regimen for CF. This treatment pattern was consistently predominant in IQVIA DA Germany (75.00%), and the NLHR registry (77.87%) (**Figure 4, Figure 5**).

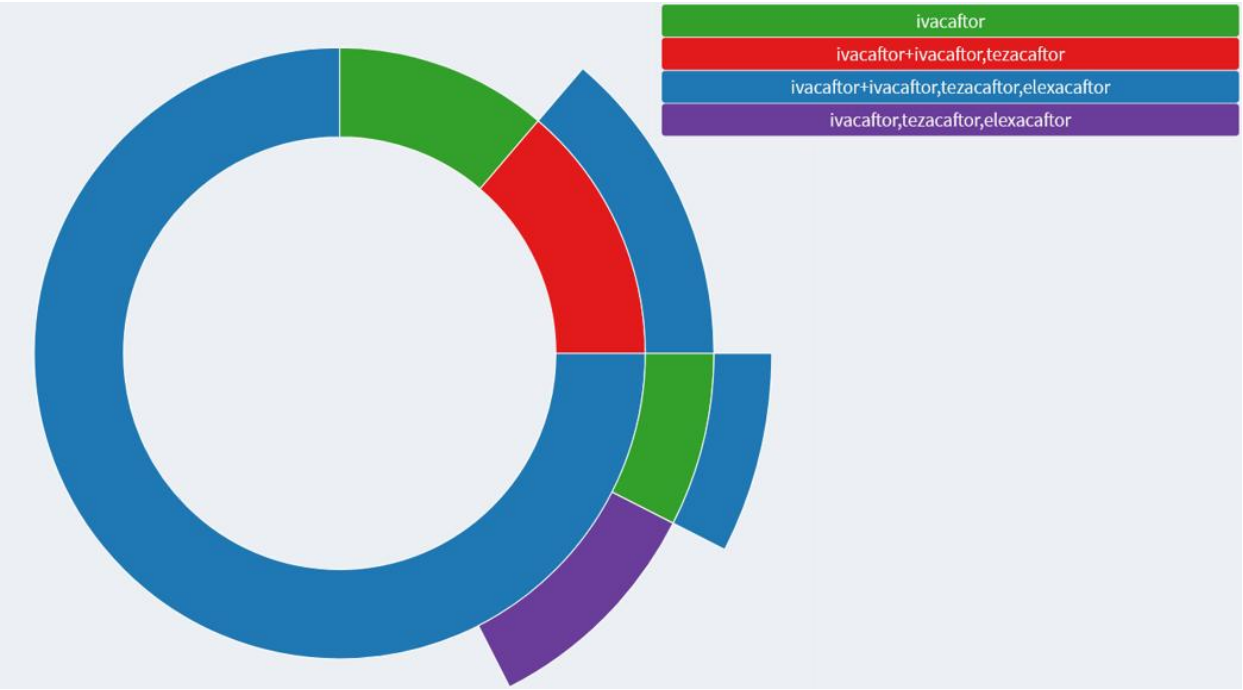
Other first-line treatments varied by data source. In IQVIA DA Germany, 11.25% of individuals received ivacaftor alone, while 13.75% initiated a combination of ivacaftor and a fixed-dose product of ivacaftor and tezacaftor. In the NLHR registry, 15.57% initiated therapy with ivacaftor and lumacaftor, 4.51% with ivacaftor alone, and 2.05% with a fixed-dose combination of ivacaftor, tezacaftor and elexacaftor product.

Switching between CFTR modulator therapies was infrequent. In IQVIA DA Germany, all individuals who initiated treatment with the combination of ivacaftor and a fixed-dose product of ivacaftor and tezacaftor subsequently switched to the combination of ivacaftor and a fixed-dose product ivacaftor, tezacaftor, and elexacaftor. Additionally, 10.00% of the individuals initiating treatment with the combination of ivacaftor and a fixed-dose product ivacaftor, tezacaftor, and elexacaftor switched to fixed-dose product of ivacaftor, tezacaftor, and elexacaftor alone, while 7.5% switched to ivacaftor alone before later switching back to their initial first-line treatment.

In the NLHR registry, 13.11% of individuals switched from a combination therapy of ivacaftor and fixed-dose product of ivacaftor, tezacaftor, and elexacaftor to fixed-dose product of ivacaftor, tezacaftor, and elexacaftor alone, and 2.87% switched back to initial first-line treatment. Among those treated with ivacaftor and lumacaftor, 4.92% transitioned to a regimen including ivacaftor and lumacaftor plus ivacaftor and ivacaftor, tezacaftor and elexacaftor, while 4.10% switched directly to the combination of ivacaftor and a fixed-dose product of ivacaftor, tezacaftor, and elexacaftor.

No plots were generated for CPRD GOLD due to small numbers in the overall cohort that cause treatment pathways to be obscured.

Sankey diagrams and plots visualising the duration of treatment episodes, including median duration of the first line therapy, are available in the Shiny application.

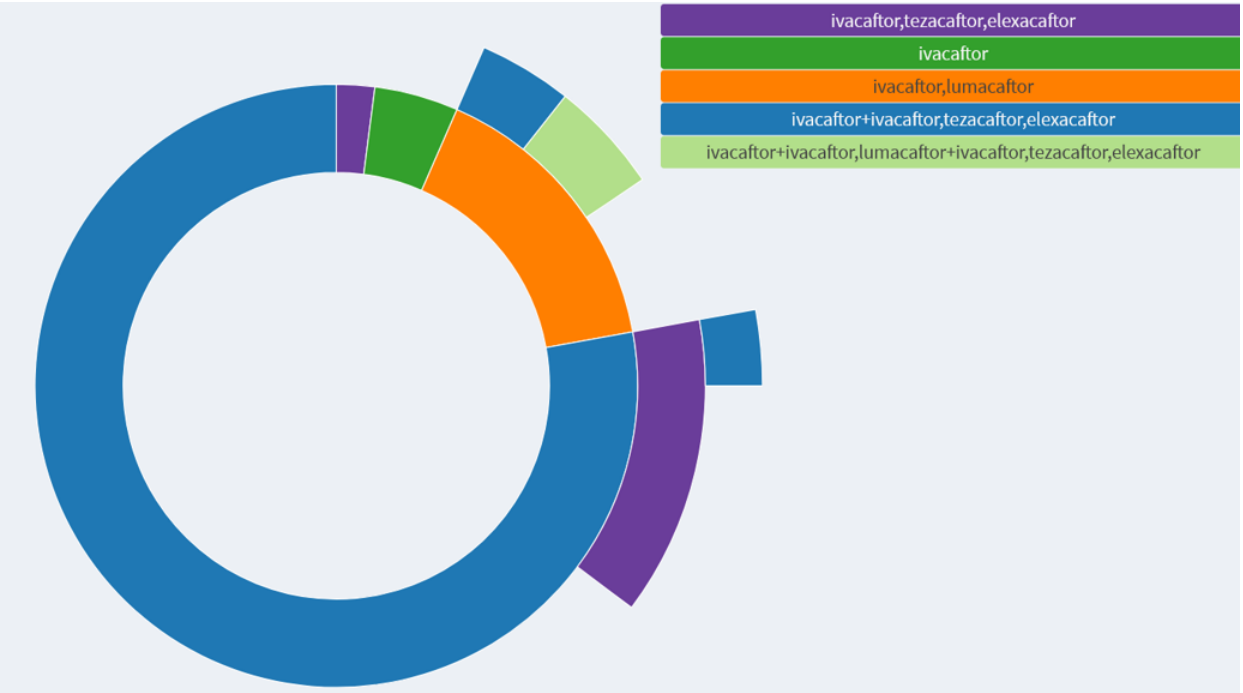


	Pathway	Combination	Line	Percentage
1	ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	1	75.00%
2	ivacaftor+ivacaftor,tezacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor	1	13.75%
2	ivacaftor+ivacaftor,tezacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	2	13.75%
3	ivacaftor	ivacaftor	1	11.25%
4	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	2	10.00%
5	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor	2	7.50%
5	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	3	7.50%

Figure 4. Sunburst plot of CFTR treatment in IQVIA DA Germany.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments, and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific CFTR modulator regimens, as shown in the legend. The accompanying table provides detailed counts and percentages for each pathway.

Treatment pathways were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort that initiated that drug/drug combination.



	Pathway	Combination	Line	Percentage
1	ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	1	77.87%
2	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	2	13.11%
3	ivacaftor,lumacaftor	ivacaftor,lumacaftor	1	15.57%
4	ivacaftor,lumacaftor-ivacaftor+ivacaftor,lumacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,lumacaftor+ivacaftor,tezacaftor,elexacaftor	2	4.92%
5	ivacaftor	ivacaftor	1	4.51%
6	ivacaftor,lumacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	2	4.10%
7	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	3	2.87%
8	ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	1	2.05%

Figure 5. Sunburst plot of CFTR treatment in NLHR.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments, and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific CFTR modulator regimens as shown in the legend. The accompanying table provides detailed counts and percentages for each pathway.

Treatment pathways were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort that initiated that drug/drug combination.

Treatment pattern results for the paediatric population were only available for the NLHR registry (**Figure S1** in **ANNEX III**). In the NLHR, the most frequently observed first-line therapy was a combination of ivacaftor and fixed-dose product of ivacaftor, tezacaftor and elexacaftor (81.82%), followed by fixed-dose combination product of ivacaftor and lumacaftor (18.18%). Among paediatric patients initiating the combination of ivacaftor and fixed-dose product of ivacaftor, tezacaftor and elexacaftor, 9.09% subsequently switched to fixed-dose product of ivacaftor, tezacaftor and elexacaftor alone (**Figure S1** in **ANNEX III**). Data from other data sources (IQVIA DA Germany, CPRD GOLD) were not displayed due to small sample sizes and suppression of counts to preserve confidentiality.

In the adult population, treatment pathways were consistent with the overall analysis in IQVIA DA Germany and NLHR (**Figure S2–Figure S3** in **ANNEX III**). The most common first-line therapies mirrored those observed in the total study population, with the combination of ivacaftor and fixed-dose product of ivacaftor, tezacaftor and elexacaftor being predominant. Results from CPRD GOLD were not reported due to low sample sizes and data suppression.

Sankey diagrams are available in the Shiny application.

13.4. Characterisation of CFTR modulator treatment

13.4.1. Treatment characterisation overall

Treatment episodes were defined using multiple gap era thresholds (30, 60, and 120 days) to evaluate the robustness of exposure estimates. The results are presented based on the 120-day gap definition. Comparative results using 30- and 60-day gaps are available in the accompanying Shiny application for reference.

The median duration of exposure to any CFTR modulator varied across data sources. In hospital-based data sources, median exposure ranged from 4 days in CDW Bordeaux, 5 days in APHM, and 9 days in POLIMI to up 366 days in H12O (**Table 16**). In contrast, longer durations are observed in primary care and registry data sources, with median exposure reaching 679 days in IQVIA DA Germany and 539 days NLHR (**Table 16**).

Median counts of repeated exposure episodes ranged from 1 in CPRD GOLD, 2 in APHM and H12O to 18 in NLHR and 19 in IQVIA DA Germany. Cumulative dose estimates for ivacaftor varied widely across data sources. Median cumulative doses ranged from 2,000 mg in APHM, 4,200 mg in CPRD GOLD to 36,179 mg in NLHR and 75,600 mg in IQVIA DA Germany. Cumulative dose data were not available in CDW Bordeaux, H12O, and POLIMI. For lumacaftor, a cumulative dose of 1,600 mg was reported in APHM.

Characteristics of CFTR modulator treatment differed by age groups and data source. Among the paediatric population on CFTR modulator treatment, median exposure duration in hospital-based data sources ranged from 4 days in CDW Bordeaux, 5 days in APHM, 7 days in POLIMI, to 15 days in H12O (**Table 17**). In primary care data source and registry, the median duration of exposure ranged from 201 days in IQVIA DA Germany and 506 days in NLHR. Median counts of repeated exposure episodes ranged from 2 in APHM, H12O and POLIMI, to 5 in IQVIA DA Germany, 6 in CDW Bordeaux, and 18 in the NLHR. Median cumulative ivacaftor dose ranged from 1,750 mg in APHM to 25,200 mg in NLHR. Cumulative dose was not available in CDW Bordeaux, H12O, and POLIMI. Median lumacaftor cumulative dose was 1,600 mg in APHM. Cumulative dose estimates for lumacaftor in other data sources, as well as for tezacaftor and elexacaftor in children, were limited or unavailable.

In the adult population, exposure duration was generally longer and more variable, with median exposed days ranging from 4 days in CDW Bordeaux, 6 days in APHM, 9 days in POLIMI, to 366 days in H12O, 546 days in the NLHR and 731 days in IQVIA DA Germany (**Table 17**). Median cumulative ivacaftor dose ranged from 2,000 mg in APHM to 92,400 mg in IQVIA DA Germany. Cumulative dose data were not available for CDW Bordeaux, H12O, and POLIMI. Median lumacaftor cumulative dose was 800 mg in APHM, and tezacaftor was 2,800 mg in IQVIA DA Germany.

Table 16. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulators (any CFTR modulator), presented for the overall population and by data source, 2015–2024.

Variable name	Estimate name	Additional level	CDM name						
			APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Number of subjects	N	Overall	82	96	171	107	273	59	13
Number of exposures	Median [q25–q75]	Any CFTR modulator	2 [1–2]	6 [3–14]	19 [4–49]	7 [2–18]	18 [12–26]	2 [1–4]	1 [1–2]
	Range	Any CFTR modulator	1 to 13	1 to 222	1 to 102	1 to 55	1 to 78	1 to 11	1 to 2
Days exposed	Median [q25–q75]	Any CFTR modulator	5 [3–12]	4 [2–8]	679 [128–1,539]	9 [6–15]	539 [425–552]	366 [42–440]	28 [1–28]
	Range	Any CFTR modulator	1 to 138	1 to 725	19 to 2,907	1 to 147	42 to 2,157	2 to 1,500	1 to 28
Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	2,000 [1,000–3,500]	-	75,600 [12,600–230,550]	-	36,179 [13,668–42,840]	-	4,200 [300 - 8,400]
	Range	Ivacaftor	150 to 30,600	-	0 to 734,850	-	0 to 356,116	-	150 to 16,800
	Median [q25–q75]	Lumacaftor	1,600 [0–3,800]	-	0 [0–0]	-	-	-	0 [0–0]
	Range	Lumacaftor	0 to 28,400	-	0 to 336,000	-	-	-	0 to 11,200
	Median [q25–q75]	Tezacaftor	0 [0–300]	-	0 [0–25,200]	-	-	-	0 [0–100]
	Range	Tezacaftor	0 to 10,200	-	0 to 148,400	-	-	-	0 to 5,600
	Median [q25–q75]	Elexacaftor	0 [0–600]	-	0 [0–16,800]	-	-	-	-
	Range	Elexacaftor	0 to 20,400	-	0 to 201,600	-	-	-	-

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, q25–q75 = 25th and 75th percentiles (interquartile range), range = minimum and maximum observed values. Cumulative dose is calculated for available drug components. "-" indicates that data was not available in the data source.

Table 17. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulators (any CFTR modulator), stratified by paediatric and adult populations, per data source, 2015–2024.

Age group	Variable name	Estimate name	Additional level	CDM name						
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
<18	Number of subjects	N	overall	43	57	14	23	97	11	<5
	Number of exposures	Median [q25–q75]	Any CFTR modulator	2 [1–2]	6 [2–14]	5 [1–19]	2 [1–4]	18 [12–25]	2 [1–2]	-
		Range	Any CFTR modulator	1 to 8	1 to 222	1 to 86	1 to 26	1 to 69	1 to 11	-
	Days exposed	Median [q25–q75]	Any CFTR modulator	5 [3–11]	4 [2–10]	201 [29–806]	7 [6–14]	506 [413–547]	15 [4–25]	-
		Range	Any CFTR modulator	1 to 129	1 to 725	28 to 2,176	1 to 22	57 to 2,147	2 to 155	-
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	1,750 [826–2,938]	-	10,850 [2,625–52,500]	-	25,200 [8,400–39,900]	-	-
		Range	Ivacaftor	150 to 30,600	-	0 to 734,850	-	0 to 306,600	-	-
		Median [q25–q75]	Lumacaftor	1,600 [0–3,600]	-	0 [0–5,600]	-	-	-	-
		Range	Lumacaftor	0 to 28,400	-	0 to 336,000	-	-	-	-
		Median [q25–q75]	Tezacaftor	0 [0–75]	-	0 [0–0]	-	-	-	-
		Range	Tezacaftor	0 to 10,200	-	0 to 0	-	-	-	-
		Median [q25–q75]	Elexacaftor	0 [0–150]	-	0 [0–0]	-	-	-	-
		Range	Elexacaftor	0 to 20,4000	-	0 to 0	-	-	-	-
>= 18	Number of subjects	N	overall	39	39	157	84	176	48	12

Age group	Variable name	Estimate name	Additional level	CDM name						
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
	Number of exposures	Median [q25–q75]	Any CFTR modulator	2 [1–2]	6 [4–14]	20 [4–50]	12 [3–21]	18 [12–26]	2 [1–4]	1 [1–2]
		Range	Any CFTR modulator	1 to 13	1 to 71	1 to 102	1 to 55	2 to 78	1 to 10	1 to 2
	Days exposed	Median [q25–q75]	Any CFTR modulator	6 [4–12]	4 [2–8]	731 [162–1,547]	9 [6–16]	546 [442–552]	366 [366–572]	14 [1–28]
		Range	Any CFTR modulator	1 to 138	1 to 153	19 to 2,907	1 to 147	42 to 2,157	8 to 1,500	1 to 28
	Cumulative dose milligram	Median [q25–q75]	Ivacaftor	2,000 [1,500–3,875]	-	92,400 [12,600–235,350]	-	38,211 [27,137–44,100]	-	4,200 [300–8,400]
		Range	Ivacaftor	188 to 15,075	-	0 to 623,250	-	0 to 356,116	-	150 to 16,800
		Median [q25–q75]	Lumacaftor	800 [0–3,600]	-	0 [0 - 0]	-	-	-	0 [0–0]
		Range	Lumacaftor	0 to 16,000	-	0 to 22,400	-	-	-	0 to 11,200
		Median [q25–q75]	Tezacaftor	0 [0–550]	-	2,800 [0–33,600]	-	-	-	50 [0–250]
		Range	Tezacaftor	0 to 10,050	-	0 to 148,400	-	-	-	0 to 5,600
		Median [q25–q75]	Elexacaftor	0 [0–1,100]	-	0 [0–16,800]	-	-	-	-
		Range	Elexacaftor	0 to 20,100	-	0 to 201,600	-	-	-	-

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, q25–q75 = 25th and 75th percentiles (interquartile range), range = minimum and maximum observed values. Cumulative dose is calculated for available drug components. "-" indicates that data was not available in the data source.

13.4.2. Treatment characterisation by CFTR active ingredient

Treatment duration, repeated prescriptions, and cumulative dose varied substantially across CFTR modulators and data sources (**Table S18–Table S21** in **ANNEX II**).

For ivacaftor, in the overall population, median exposure ranged from 4 days in CDW Bordeaux to 500 days in NLHR and 556 days in IQVIA DA Germany (**Table S18** in **ANNEX II**). Median counts of repeated exposure episodes ranged from 1 in APHM, H12O, and CPRD GOLD to 12 in IQVIA DA Germany. Median cumulative dose estimates varied from 750 mg in APHM to 75,600 mg in IQVIA DA Germany. In the paediatric populations, median exposure ranged from 3 days in APHM to 447 days in NLHR, with median cumulative dose between 300 mg in APHM and 31,500 mg in NLHR. In adults, median exposure ranged from 4 days in CDW Bordeaux to 524 days in NLHR and 679 days in IQVIA DA Germany, with cumulative dose up to 88,200 mg in IQVIA DA Germany.

For fixed-dose ivacaftor and lumacaftor combination products, hospital-based data sources reported short median exposures in the overall population ranging from 3 days in CDW Bordeaux to 11 days in POLIMI, whereas the NLHR registry data showed extended median exposure up to 1,317 days (**Table S19** in **ANNEX II**). Median cumulative dose for ivacaftor was 2,034 mg in APHM and 3,200 mg for lumacaftor in APHM. In the paediatric population, median exposure ranged from 3 days in CDW Bordeaux to 13 days in POLIMI and up to 1,159 days in NLHR. Median cumulative dose of ivacaftor ranged from 2,034 mg in APHM to 24,500 mg in IQVIA DA Germany, while for lumacaftor from 3,200 mg in APHM to 19,600 mg in IQVIA DA Germany. In adults, median exposure extended to 1,543 days in NLHR with median cumulative doses constant with overall estimates.

Use of fixed-dose ivacaftor and tezacaftor combination products was limited, with median durations of 1 day in CPRD GOLD and 338 days in IQVIA DA Germany in the overall population (**Table S20** in **ANNEX II**). Median cumulative dose of ivacaftor ranged from 600 mg in CPRD GOLD to 46,200 mg in IQVIA DA Germany, while for tezacaftor from 400 mg in CPRD GOLD to 30,800 mg in IQVIA DA Germany. No paediatric users were observed, while adult estimates aligned with overall results.

The fixed-dose product of ivacaftor, tezacaftor, and elexacaftor had median exposure reaching 647 days in the overall population of IQVIA DA Germany (**Table S21** in **ANNEX II**). Median cumulative dose was available in APHM. In paediatric population, median exposure ranged from 3 days in APHM to 7 days in H12O, and up to 483 days in NLHR. In adult population, median days exposed extended to 693 days in IQVIA DA Germany.

13.5. Background incidence rates of pre-specified adverse events

13.5.1. Incidence rates of anxiety among CFTR treated individuals

The occurrence of anxiety among individuals treated with any CFTR modulator therapy (plain or fixed-dose combination products) was assessed across seven data sources. Overall, the event was rare, with most data sources reporting no event or fewer than five (**Table 18**). The NLHR registry was the only data source reporting 13 events over 389 PYs, corresponding to an overall incidence rate of 33.4 per 1,000 PYs (95% CI: 17.8–57.2). Other sources, including IQVIA DA Germany and CDW Bordeaux, reported fewer than five events, while APHM, POLIMI, H12O, and CPRD GOLD recorded no events.

When stratified by active ingredient, 7 anxiety events were observed in individuals treated with the fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor in NLHR, with an overall incidence rate of 30.4 per 1,000 PYs (95% CI: 12.2–62.6) (**Table S22** in **ANNEX II**). Annual stratification was not informative due to the very low number of events.

Stratification by age group showed that paediatric populations consistently reported no event or fewer than five, while sporadic counts were observed in adults, particularly in NLHR. More detailed stratified results are available in the interactive dashboard: EUPAS1000000708.

Table 18. Incidence rate of pre-specified adverse event anxiety in CFTR modulator treated individuals (any CFTR, plain or combination drugs) in the overall study population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
APHM	82	0	2	0	0; 1,897.57
CDW Bordeaux	87	<5	1	NA	NA
IQVIA DA Germany	166	<5	161	NA	NA
POLIMI	107	0	3	0	0; 1,166.63
NLHR	257	13	389	33.42	17.8; 57.16
H12O	56	0	55	0	0; 67.15
CPRD GOLD	13	0	1	0	0; 6670.67

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

13.5.2. Incidence rates of cataract among CFTR treated individuals

Cataract was rarely observed across all data sources (**Table 19**). In the overall analysis, either no event or fewer than five events were recorded, resulting in incidence rates of zero or non-estimable values. Stratification by active ingredient showed a consistent pattern, with no event or suppressed counts due to less than five events across all CFTR modulator therapies (**Table S23** in **ANNEX II**). Age stratified analyses mirrored these findings, with both paediatric and adult cohorts showing either zero event or counts below the reporting threshold (EUPAS1000000708).

Table 19. Incidence rate of pre-specified adverse events cataract in CFTR modulator treated individuals (any CFTR, plain or combination drugs) in the overall study population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
APHM	82	0	2	0	0; 1,897.57
CDW Bordeaux	96	0	1	0	0; 2,790.38
IQVIA DA Germany	171	0	163	0	0; 22.60
POLIMI	107	0	3	0	0; 1,166.63
NLHR	270	<5	422	NA	NA
H12O	59	0	57	0	0; 64.74
CPRD GOLD	13	0	1	0	0; 6,670.67

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

13.5.3. Incidence rates of depression among CFTR treated individuals

Depression was infrequently observed across all data sources. Consistent with the pattern seen for cataract, either no incident event or fewer than five incident events were recorded in each data source, resulting in incidence rates that were either zero or not estimable (**Table 20**). This trend persisted across all stratified analyses, including by active ingredient and age group, with suppressed or absent counts (**Table S24** in **ANNEX II)** (EUPAS1000000708).

Table 20. Incidence rate of pre-specified adverse events depression in CFTR modulator treated individuals (any CFTR, plain or combination drugs) in the overall study population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
APHM	81	0	2	0	0; 1,996.15
CDW Bordeaux	95	0	1	0	0; 2,930.01
IQVIA DA Germany	168	0	163	0	0; 22.63
POLIMI	107	0	3	0	0; 1,166.63
NLHR	266	<5	420	NA	NA
H12O	55	<5	50	NA	NA
CPRD GOLD	13	0	1	0	0; 6,670.67

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

13.5.4. Incidence rates of haemoptysis among CFTR treated individuals

Across all data sources, haemoptysis was either not observed or occurred in fewer than five cases among individuals treated with any CFTR modulator treatment (**Table 21**). Due to the low event counts, incidence rates could not be estimated. CDW Bordeaux was exception, where five events were recorded over one person-year of follow-up, resulting in an incidence rate of 4,845 per 1,000 PYs (95% CI: 1,573.2–11,306.5)

(**Table 21**). Stratification by active ingredient and calendar year were not informative due to the very low number of events (**Table S25** in **ANNEX II**).

Age-stratified analysis showed no recorded haemoptysis event among paediatric patients in any data source or treatment group, while findings in adult populations were consistent with the overall results (EUPAS1000000708).

Table 21. Incidence rate of pre-specified adverse events haemoptysis in CFTR modulator treated individuals (any CFTR, plain or combination drugs) in the overall study population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Haemoptysis					
APHM	78	<5	2	NA	NA
CDW Bordeaux	89	5	1	4,844.96	1,573.15; 11,306.52
IQVIA DA Germany	171	0	163	0	0; 22.60
POLIMI	104	<5	3	NA	NA
NLHR	272	<5	421	NA	NA
H12O	54	0	54	0	0; 68.40
CPRD GOLD	13	0	1	0	0; 6,670.67

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

13.6. Incidence rates of pulmonary exacerbation

Incidence rates were only reported for data sources with sufficient follow-up time and event counts. For hospital-based data sources with zero PYs or suppressed event counts, incidence rates were excluded or suppressed to avoid unstable estimates. The NLHR registry was the only source with data to support incidence rate estimation. In NLHR, the incidence rate of pulmonary exacerbation following initiation of any CFTR modulator was 136.06 per 1,000 PYs during the first year and 288.77 per 1,000 PYs in the second-year post-initiation based on only 6 events (**Table 22**). Ingredient-specific estimates were available for fixed-dose ivacaftor, tezacaftor, and elexacaftor products (148.82 per 1,000 PYs in year one and 128.32 per 1,000 PYs in year two) (**Table S26** in **ANNEX II**).

Stratified analyses by age group were not reported due to low event counts in paediatric and adult strata or not sufficient follow-up time across most data sources. These results are available in the Shiny application (EUPAS1000000708).

Table 22. Incidence rate of pulmonary exacerbation following any CFTR modulator initiation, one and two years post any CFTR modulator initiation, overall.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
One year post initiation					
APHM	9	6	0	-	-
CDW Bordeaux	6	5	0	-	-
IQVIA DA Germany	169	<5	89	NA	NA

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
POLIMI	39	29	0	-	-
NLHR	201	13	96	136.06	72.45; 232.67
H12O	11	<5	0	NA	NA
CPRD GOLD	NA	0	NA	0	0
Two-year post initiation					
APHM	11	8	0	-	-
CDW Bordeaux	11	10	0	-	-
IQVIA DA Germany	56	0	38	0	0; 96.70
POLIMI	16	15	0	-	-
NLHR	64	6	21	288.77	105.98; 628.52
H12O	45	<5	37	NA	NA
CPRD GOLD	12	0	0	-	-

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

13.7. Sensitivity analysis

To assess the robustness of incidence rate estimates for pre-specified adverse events of special interest, a sensitivity analysis was conducted across all participating data sources. This analysis excluded the CFTR modulator treatment end as a censoring criterion *(objectives 4, 5)*.

For anxiety, the sensitivity analysis revealed measurable incidence in the overall study population of NLHR and CDW Bordeaux treated with any CFTR modulator (**Table 23**). NLHR reported 18 events following treatment initiation of any CFTR modulator treatment, yielding an overall incidence rate of 34.25 per 1,000 PYs, while CDW Bordeaux recorded 18 events with an incidence rate of 60.20 per 1,000 PYs. Age-stratified analysis showed that the majority of anxiety events in CDW Bordeaux were recorded in paediatric patients (12 events; incidence rate: 80.57 per 1,000 PYs), with the remainder in adults (6 events; incidence rate: 56.46 per 1,000 PYs). In NLHR, 15 of the 18 anxiety events occurred in adults, corresponding to an incidence rate of 43.10 per 1,000 PYs (EUPAS1000000708).

Event counts for cataract and depression were in line with the primary analysis.

Following removal of the treatment-end censoring, additional haemoptysis events were identified in APHM, POLIMI, and CDW Bordeaux, among individuals treated with any CFTR modulator treatment (**Table 23**). Across these sources, overall incidence rates ranged from 18.74 per 1,000 PYs in POLIMI, 35.95 per 1,000 PYs in APHM to 60.41 per 1,000 PYs in CDW Bordeaux. Stratification by age showed that the majority of haemoptysis events occurred in adults (EUPAS1000000708).

Table 23. Incidence rate of anxiety and haemoptysis following any CFTR modulator treatment initiation in the overall study population, per data source (sensitivity analysis).

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Anxiety					
APHM	82	<5	287	NA	NA
CDW Bordeaux	87	18	299	60.20	35.68
IQVIA DA Germany	166	<5	800	NA	NA
POLIMI	107	0	349	0	0
NLHR	257	18	525	34.25	20.30
H12O	56	<5	144	NA	NA
CPRD GOLD	13	0	49	0	0
Haemoptysis					
APHM	78	9	250	35.95	16.44; 68.25
CDW Bordeaux	89	17	281	60.41	35.19; 96.72
IQVIA DA Germany	171	0	820	0	0; 4.50
POLIMI	104	6	320	18.74	6.88; 40.78
NLHR	272	<5	572	NA	NA
H12O	54	<5	134	NA	NA
CPRD GOLD	13	0	49	0	0; 74.87

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person-years, CI = confidence interval.

Sensitivity analyses at the active ingredient level confirmed that incidence rates for depression, cataract, and anxiety were consistent with those observed for any CFTR modulator. Similarly, haemoptysis incidence by ingredient aligned with the overall findings, with the incidence rates observed in CDW Bordeaux, followed by APHM and POLIMI. Events were predominantly recorded in adults, reinforcing the age-stratified trends seen in the primary analysis (EUPAS1000000708).

Sensitivity analysis for pulmonary exacerbation yielded results broadly consistent with the primary analysis. In NLHR, incidence rates for any CFTR modulator treatment were slightly lower when the CFTR modulator treatment end was excluded as a censoring criterion in the sensitivity analysis, with 131.86 per 1,000 PYs in year one and 111.14 per 1,000 PYs in year two. For fixed-dose ivacaftor, tezacaftor, and elexacaftor products, incidence rates were 147.61 per 1,000 PYs in year one and 126.95 per 1,000 PYs in year two (EUPAS1000000708).

In addition to the censoring adjustment, a separate sensitivity analysis was conducted to treatment pattern and drug utilisation metrics, applying alternative gap definitions. The gaps variations were chosen to reflect scenarios where prescription records might be incomplete or delayed.

14. DISCUSSION

14.1. Key results

Participants

A total of 801 individuals with a prescription record for any CFTR modulator therapy during the study period were included across seven European data sources. The largest contributions were from NLHR (34.08%) and IQVIA DA Germany (21.35%). Ivacaftor was prescribed to 506 individuals, while the fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor was prescribed to 398 individuals. However, prescription records did not allow clear differentiation between ivacaftor used as true monotherapy and ivacaftor used as part of the combination therapy including fixed-dose ivacaftor, tezacaftor, and elexacaftor triple therapy. The fixed-dose combination of ivacaftor and lumacaftor was prescribed to 229 individuals, primarily in hospital-based sources. Ivacaftor and tezacaftor combination products were infrequently prescribed (n=43), with 86% of cases reported from IQVIA DA Germany.

Patient-level characterisation of CFTR modulator users

Median age at first prescription record for any CFTR modulator during the study period ranged from 16 years in APHM and CDW Bordeaux to 34 years in CPRD GOLD. The highest proportion of paediatric prescriptions was observed in CDW Bordeaux (59.38%) and APHM (52.44%), whereas adult prescriptions predominated in IQVIA DA Germany (91.81%) and CPRD GOLD (92.31%). A higher proportion of females was observed across most hospital-based and primary care data sources, ranging from 52.34% in POLIMI to 64.41% in H12O, except in NLHR registry where males accounted for 53.85%. Age and sex distributions varied by active ingredient, with fixed-dose ivacaftor and tezacaftor combination products used exclusively in adults, while fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor was prescribed across both age groups. Use of supportive therapies (e.g., mucolytics, salbutamol, pancreatic enzymes) was highest prior to CFTR modulator initiation, declined at treatment start, and either stabilised or increased following initiation. These temporal patterns were consistent across age groups, data sources, and CFTR modulators.

Treatment patterns

Treatment episodes were constructed using a 120-day gap to account for potential delays in prescription refills, ensuring robust capture of treatment continuity. The most common first-line CFTR modulator treatment was a combination of ivacaftor together with a fixed-dose product of ivacaftor, tezacaftor, and elexacaftor, which together constitute the recommended combination regimen for cystic fibrosis. This treatment pattern was consistently predominant in NLHR (77.87%), IQVIA DA Germany (75.00%). Other first-line treatments varied by data source, with ivacaftor, combinations of ivacaftor and tezacaftor, or ivacaftor and lumacaftor observed in smaller proportions. Switching between CFTR modulator therapies was infrequent. When switching occurred, most transitions were to a combination of ivacaftor together with a fixed-dose product of ivacaftor, tezacaftor, and elexacaftor.

Characterisation of CFTR modulator treatment

Treatment episodes were defined using a 120-day gap to ensure robust estimation of CFTR modulator exposure, accounting for potential delays in prescription refills. Median exposure durations of any CFTR modulator varied widely across data sources and treatment types, ranging from 4 days in CDW Bordeaux, 5 days in APHM, and 9 days in POLIMI to up 366 days in H12O, 679 days in IQVIA DA Germany and 539 days in NLHR. Median counts of repeated exposure episodes ranged from 1 in CPRD GOLD, 2 in APHM and H12O to 18 in NLHR and 19 in IQVIA DA Germany. Cumulative dose estimates varied widely across data sources and ingredients. Among paediatric patients, median exposure duration ranged from 4–15 days in hospital-based sources and 201–506 days in registry/primary care sources. In adults, median exposure duration ranged from 4–366 days (hospital-based) to 546–731 days (registry/primary care).

Treatment duration, repeated prescriptions, and cumulative dose varied substantially across CFTR modulators and data sources. Exposure durations were generally shorter in paediatric populations and longer in adults. Cumulative dose estimates for some CFTR modulators and data sources were limited.

Background incidence rates of pre-specified adverse events

Adverse events including anxiety, cataract, depression, and haemoptysis were uncommon across all CFTR modulator cohorts and data sources. Most data sources reported no events or fewer than five. Incidence rates could only be estimated for anxiety in the NLHR registry, with 13 events over 389 PYs (incidence rate: 33.4 per 1,000 PYs, 95% CI: 17.8–57.2), primarily among adults treated with a fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor. Cataract, depression, and haemoptysis were either not observed or occurred at non-reportable levels (<5 events) across age groups or CFTR modulator types. An exception was CDW Bordeaux, which reported five haemoptysis events over one PY (4,845 per 1,000 PYs; 95% CI: 1,573.2–11,306.5).

Incidence rates of pulmonary exacerbation

Incidence rates for pulmonary exacerbations were only reported for data sources with sufficient follow-up time and event counts. The NLHR registry was the sole source with data, reporting an incidence rate of 136.06 per 1,000 PYs in the first year following CFTR modulator initiation and 288.77 per 1,000 PYs in the second year. Ingredient-specific estimates were available for fixed-dose ivacaftor, tezacaftor and elexacaftor combination products in NLHR (148.82 per 1,000 PYs in year one and 128.32 per 1,000 PYs in year two).

Sensitivity analysis

A sensitivity analysis was conducted excluding CFTR modulator treatment end as a censoring criterion to assess the robustness of adverse event incidence estimates. Anxiety was the event with measurable incidence in multiple sources: NLHR reported 18 events (incidence rate: 34.3 per 1,000 PYs) and CDW Bordeaux also reported 18 events (incidence rate: 60.2 per 1,000 PYs) in the overall study population treated with any CFTR modulator during the study period, with paediatric patients accounting for the majority in CDW Bordeaux. Sensitivity analyses for cataract or depression yielded results consistent with the primary analysis. Incidence rates for haemoptysis increased slightly following removal of censoring criterion, ranging from 18.74 per 1,000 PYs in POLIMI to 60.41 per 1,000 PYs in CDW Bordeaux, primarily among adults. Other data sources reported zero or suppressed counts. For pulmonary exacerbation, NLHR reported an incidence rates of 131.86 per 1,000 PYs in year one and 111.14 per 1,000 PYs in year two, while for ivacaftor, tezacaftor, and elexacaftor combination products, incidence rates were 147.61 per 1,000 PYs in year one and 126.95 per 1,000 PYs in year two post initiation.

14.2. Limitations of the research methods

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

Data sources/setting: This study utilised data from 7 sources: APHM, CDW Bordeaux, IQVIA DA Germany, POLIMI, NLHR, H12O, and CPRD GOLD. The results derived from these data sources may not be representative of diagnoses and prescriptions in other countries or data sources. Variations in results were 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, in some data sources, such as APHM, CDW Bordeaux, POLIMI, IQVIA DA Germany, and H12O, the last interaction with the healthcare system is used 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.

Drug prescriptions: A recorded prescription did not necessarily indicate that the patient actually took the drug. Therefore, assumptions of actual use were made. In hospital-based sources such as APHM, CDW Bordeaux, H12O, and POLIMI, prescriptions were typically recorded only during hospital inpatient stays. Outpatient prescriptions were not captured, limiting visibility into long-term therapy. In contrast, NLHR captured outpatient prescriptions but lacked inpatient prescription data. These differences may lead to incomplete exposure ascertainment, which could bias incidence rate estimates, particularly when denominators were based on limited follow-up time. In IQVIA DA Germany records of CFTR modulator treatment prescriptions were limited considering the size of the country and the expected prevalence of cystic fibrosis. This data source included primary care and office-based specialist practices, however, individuals with cystic fibrosis are usually treated in specialised hospital settings or hospital outpatient clinics, where CFTR modulator therapies are prescribed. Similarly, in CPRD GOLD, records of CFTR modulator treatment prescriptions were low. CPRD GOLD is a primary care data source and CFTR therapies are not prescribed by GPs but by specialists at CF centres within hospitals.

Phenotype of pulmonary exacerbation: Outcome of interest was defined based on standard concept IDs. Diagnostic codes might not capture subclinical cases, often lack granularity on disease severity, and could vary across healthcare settings. The definition of pulmonary exacerbation used in this study included outpatient visits with a respiratory diagnosis and an oral antibiotic prescription. This criterion may capture maintenance therapy or treatment for mild infections rather than true exacerbations, potentially leading to overestimation. Conversely, exacerbations coded under non-specific terms or treated at home without healthcare visits may not be captured. These limitations should be considered when interpreting the results.

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 were not displayed for governance reasons when the number of events is <5. Incomplete capture of outcomes may lead to underestimation of incidence of adverse events of interest. For example, POLIMI captured only outcome records during hospital inpatient episodes and outcomes in outpatient settings were not available.

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 used 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 differed substantially from the imputed values. Additionally, treatment duration may be underestimated when patients transition between care settings, as these changes were not always fully captured in the data. Exposure duration estimates derived from hospital-based data sources should be interpreted with caution, as these sources capture only short inpatient episodes and did not reflect the full duration of long-term CFTR modulator therapy, which continues outside the hospital settings. Consequently, exposure durations from these sources underestimated true treatment duration and should not be considered indicative of actual long-term use.

Treatment episode was defined using a 30-day, 60-day, and 120-day gap between prescriptions. Treatment episode using 120-day gap was used to account for delayed refills. While this approach is commonly applied in drug utilisation studies, it may overestimate treatment duration in settings with shorter refill intervals. Sensitivity analyses using alternative gap lengths were also performed and could provide additional context.

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 were crucial for defining possible treatment pathways, i.e., which treatment eras were considered as a separate treatment, as a combination treatment, or were 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.

Study period: Part of the study period coincided with the COVID-19 pandemic (2020–2022), which likely affects rates of outcomes due to changes in healthcare use.

14.3. Interpretation

This multi data source study provides a comprehensive characterisation of CFTR modulator use, treatment patterns, and pre-specified outcomes among individuals diagnosed with CF across seven European data sources.

We identified 801 individuals with CFTR modulator prescriptions during the study period. This count appears lower than expected given the prevalence of cystic fibrosis in the included countries, likely reflecting structural limitations in data capture rather than true treatment uptake.[18] Hospital-based sources primarily record inpatient prescriptions and miss outpatient prescriptions, while primary care datasets do not include specialist prescribing. Registry data, although more comprehensive, may not fully capture all treated patients during the study period. These factors likely contribute to underestimation of treated populations. A higher proportion of females was observed in most hospital-based and primary care data sources, contrasting with registry data where males predominated. This pattern could reflect selection toward patients with greater clinical complexity and differences in healthcare utilisation rather than true prevalence differences. Ivacaftor was prescribed to 506 individuals. When interpreting ivacaftor prescription counts, it is important to note that individual prescription records did not reliably distinguish ivacaftor used as true monotherapy from ivacaftor used as the evening component of the ivacaftor, tezacaftor, and elexacaftor triple therapy regimen. In current clinical practice, ivacaftor is predominantly combined with ivacaftor, tezacaftor, and elexacaftor rather than as monotherapy. Therefore, prescription-level counts of ivacaftor should not be interpreted as indicative of monotherapy use.

Use of supportive therapies (e.g., mucolytics, salbutamol, pancreatic enzymes) was highest prior to CFTR modulator initiation, declined at treatment start, and either stabilised or increased following initiation. These temporal patterns were consistent across age groups, data sources, and CFTR modulators. The decline in supportive therapy use near treatment initiation may reflect differential capture of data rather than true clinical trends. In hospital-based sources that primarily record inpatient prescriptions (e.g., APHM, CDW Bordeaux, H12O, POLIMI), outpatient prescriptions are not captured. Trends should be interpreted with caution, as data capture in hospital-based sources reflects only patients' hospitalisations. These individuals likely represent more severe cases, which may explain the continued or increased use of supportive therapies despite CFTR modulator treatment.

The most frequently observed first-line treatment was the combination of ivacaftor with a fixed-dose combination of ivacaftor, tezacaftor, and elexacaftor. This regimen corresponds to triple therapy, administered as a combination pill in the morning and ivacaftor in the evening, and is consistent with current clinical guidelines. The predominance of triple therapy reflects its widespread adoption as the standard of care for eligible individuals with cystic fibrosis. However, the observed proportion of individuals

on triple therapy may appear lower than expected.[18] This likely reflects several factors including the data completeness, timing of EMA approval (August 2020), and the study period ending in 2024. These considerations should be taken into account when interpreting the findings. Additionally, the CFTR modulator combination of deutivacaftor, tezacaftor, and vanzacaftor was approved by EMA in 2025, however, no routine use is expected within our study period. Future studies should incorporate this therapy to provide a more complete picture of CFTR modulator utilisation.

Interpretation of treatment patterns should be contextualised within the parameters applied to define treatment episodes and treatment sequence and the limitations of the underlying data sources. A 120-day gap was used to define treatment episodes, and it was a methodological choice, accounting for potential delays in prescription refills. Treatment pattern results presented here are based on two data sources (IQVIA DA Germany and NLHR). Hospital-based data sources were excluded because they primarily capture inpatient prescribing, whereas CFTR modulators are typically dispensed in outpatient settings. This exclusion may lead to incomplete treatment histories. Similarly, interpretation of treatment duration must consider the limitations of hospital-based data. These sources captured only short inpatient episodes and did not record outpatient prescribing or dispensing, where the majority of long-term CFTR modulator therapy occurs. Consequently, treatment duration estimates derived from hospital-based data sources underestimated true long-term use and should not be interpreted as reflective of actual treatment duration.

These limitations also affect the interpretation of adverse event rates. In hospital datasets, incidence rates may appear inflated due to short follow-up periods and small denominators, as seen with haemoptysis in CDW Bordeaux (4,845 per 1,000 PYs). Such datasets often capture only more severe cases, introducing ascertainment bias and limiting generalisability. Additionally, the absence of outpatient data and restricted look-back periods hinder the ability to distinguish incident from prevalent events. Consequently, incidence estimates from hospital-only data should be interpreted with caution.

Across all data sources, adverse events of special interest, including anxiety, cataract, depression, and haemoptysis, were rare. This aligns with published literature indicating that CFTR modulators are generally well tolerated in real-world settings. However, the rarity of events and limited sample sizes restricted the ability to generate robust stratified estimates, particularly for annual trends and ingredient-specific cohorts. Outpatient outcomes were not consistently captured in the hospital-based data sources, which may have led to underestimation of incidence rates. Sensitivity analyses confirmed the robustness of findings for cataract and depression and identified additional anxiety and haemoptysis events when treatment-end censoring was removed, and follow-up was extended beyond the end of recorded treatment. However, it remains unknown whether these events occurred during actual treatment of after treatment discontinuation and whether are related to CFTR modulator use.

CFTR modulators are generally expected to reduce pulmonary exacerbations by improving CFTR function and airway clearance, as demonstrated in clinical trials and real-world data studies. In this analysis, NLHR was the only data source with sufficient data to estimate incidence rates across both one- and two-year periods following treatment initiation. For any CFTR modulator, rates were 136.06 per 1,000 PYs in year one and 288.77 per 1,000 PYs in year two, based on only six events, resulting in a wide confidence interval and limited reliability. Differences in patient mix and follow-up time may also contribute, as older modulators (e.g., ivacaftor or ivacaftor and lumacaftor) are often prescribed to patients with more advanced disease. Ingredient-specific estimates for fixed-dose ivacaftor, tezacaftor, and elexacaftor combination products in NLHR showed a different pattern, with incidence rates of 148.82 per 1,000 PYs in year one and 128.32 per 1,000 PYs in year two. Overall, these findings underscore the importance of interpreting incidence rates in the context of sample size, patient characteristics, and treatment composition. Estimates based on small numbers should be considered exploratory and interpreted with caution.

14.4. Generalisability

While our study comprised data from 7 data sources across the European Union, and covered primary care, registry, outpatient specialist care, and inpatient care, findings from this study are not to be generalised to other countries or data sources but only reflect the situation in the specific region and setting covered by the respective data source.

15. CONCLUSION

This multi-data source cohort study provides a comprehensive characterisation of CFTR modulator use, treatment patterns, pre-specified adverse events, and pulmonary exacerbation among individuals diagnosed with cystic fibrosis across seven European data sources. The most common first-line regimen was triple therapy (ivacaftor, tezacaftor, and elexacaftor), although treatment patterns and demographic profiles varied across data sources. Adverse events were rare, with measurable incidence rates only for anxiety. Pulmonary exacerbation rates could be estimated only in the NLHR due to limitations in follow-up and event capture in other sources.

While these findings illustrate the potential of routinely collected healthcare data to inform real-world treatment patterns in cystic fibrosis, current limitations in data completeness, follow-up, population coverage, and heterogeneity in data types (hospital versus outpatient) constrained the ability to draw robust conclusions. Observed trends should therefore be regarded as exploratory rather than confirmatory. Future work should focus on improving data completeness, coverage, and availability to enable more comprehensive and reliable assessments.

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17. ANNEXES

ANNEX I: List of concept definitions

List of concept definitions for cystic fibrosis

Concept id	Concept Code	Concept Name	Descendants
3168099	15900001000004100	Arthralgia assoc with cystic fibrosis	-
44782927	698940002	Arthropathy associated with cystic fibrosis	-
44802278	526071000000104	Arthropathy in cystic fibrosis	-
42538542	762270003	Atypical cystic fibrosis	-
44805713	776981000000103	Cirrhosis associated with cystic fibrosis	-
42538541	762269004	Classical cystic fibrosis	-
441267	190905008	Cystic fibrosis	-
1245046	1296527009	Cystic fibrosis due to heterozygous deltaF508 mutation	-
1245047	1296528004	Cystic fibrosis due to homozygous deltaF508 mutation	-
3189821	18770001000004100	Cystic fibrosis exacerbation	-
4341770	235978006	Cystic fibrosis of pancreas	-
254320	86555001	Cystic fibrosis of the lung	-
36714965	720401009	Cystic fibrosis with gastritis and megaloblastic anemia syndrome	-
193174	86092005	Cystic fibrosis with meconium ileus	-
434615	81423003	Cystic fibrosis without meconium ileus	-
4143529	426705001	Diabetes mellitus associated with cystic fibrosis	-
3178281	2350001000004100	Diabetes mellitus complicating Cystic fibrosis	-
4144583	427089005	Diabetes mellitus due to cystic fibrosis	-
45768983	707536003	Digestive system manifestation co-occurrent and due to cystic fibrosis	-
37311779	817966005	Distal intestinal obstruction syndrome due to cystic fibrosis	-
44808532	859041000000103	Exacerbation of cystic fibrosis	-
45769170	707766007	Exocrine pancreatic manifestation co-occurrent and due to cystic fibrosis	-
45769019	707577004	Female infertility due to cystic fibrosis	-
37110724	725052002	Fetal cystic fibrosis	-
37396320	716088000	Follicular hamartoma with alopecia and cystic fibrosis syndrome	-
605193	1010616001	Liver cirrhosis due to classical cystic fibrosis	-
3190339	2340001000004100	Liver disease complicating cystic fibrosis	-
4141669	427022004	Liver disease due to cystic fibrosis	-
45769146	707734002	Liver enzymes level above reference range due to cystic fibrosis	-
45772934	707418001	Male infertility due to cystic fibrosis	-
45768892	707419009	Osteoporosis due to cystic fibrosis	-

Concept id	Concept Code	Concept Name	Descendants
45768987	707542004	Otorhinolaryngological manifestation co-occurrent and due to cystic fibrosis	-
45768915	707450006	Pancreatic insufficiency due to cystic fibrosis of pancreas	-
45769020	707578009	Perforation of intestine due to cystic fibrosis with meconium ileus	-
36715501	721197001	Polyneuropathy due to classical cystic fibrosis	-
45771017	707420003	Portal hypertension due to cystic fibrosis	-
3183290	13840001000004100	Pulmonary exacerbation cystic fibrosis	-
42538543	762271004	Subclinical cystic fibrosis	-

List of concept definitions for drugs of interest

CFTR modulators

Concept id	Concept Code	Concept Name	Descendants	Exclude
Any CFTR modulator				
42709323	1243041	ivacaftor	Yes	-
Ivacaftor				
42709323	1243041	ivacaftor	Yes	-
35200175	2053507	ivacaftor / lumacaftor Granule Product	Yes	Yes
36248596	1655924	ivacaftor / lumacaftor Oral Product	Yes	Yes
36248597	1655925	ivacaftor / lumacaftor Pill	Yes	Yes
963952	1999384	ivacaftor / tezacaftor Oral Product	Yes	Yes
963953	1999385	ivacaftor / tezacaftor Pill	Yes	Yes
2937581	OMOP5154281	ivacaftor 150 MG / tezacaftor 100 MG [Symdeko]	Yes	Yes
994767	OMOP4821281	ivacaftor 150 MG / tezacaftor 100 MG [Symkevi]	Yes	Yes
35898621	OMOP5042861	ivacaftor 75 MG / tezacaftor 50 MG [Symkevi]	Yes	Yes
1200983	2635011	elexacaftor / ivacaftor / tezacaftor Granule Product	Yes	Yes
1200984	2635012	elexacaftor / ivacaftor / tezacaftor Oral Granules	Yes	Yes
37497448	2257007	elexacaftor / ivacaftor / tezacaftor Oral Product	Yes	Yes
37497450	2257009	elexacaftor / ivacaftor / tezacaftor Oral Tablet	Yes	Yes
37497449	2257008	elexacaftor / ivacaftor / tezacaftor Pill	Yes	Yes
1525625	2611459	ivacaftor 94 MG / lumacaftor 75 MG [ORKAMBI]	Yes	Yes
35200184	2053518	ivacaftor 188 MG / lumacaftor 150 MG [ORKAMBI]	Yes	Yes
36787864	OMOP4776127	ivacaftor / lumacaftor Delayed Release Oral Tablet	Yes	Yes
35898626	OMOP5042866	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Kaftrio]	Yes	Yes
2937578	OMOP5154278	elexacaftor 100 MG / ivacaftor 75 MG / tezacaftor 50 MG [Trikafta]	Yes	Yes
36953601	OMOP5184428	elexacaftor 50 MG / ivacaftor 37.5 MG / tezacaftor 25 MG [Kaftrio]	Yes	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
1718095	1812469	ivacaftor 125 MG / lumacaftor 100 MG [ORKAMBI]	Yes	Yes
44119057	OMOP1113688	ivacaftor 125 MG / lumacaftor 200 MG [Orkamb]	Yes	Yes
46275585	1655930	ivacaftor 125 MG / lumacaftor 200 MG [ORKAMBI]	Yes	Yes
Ivacaftor lumacaftor				
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	-	-
1718095	1812469	ivacaftor 125 MG / lumacaftor 100 MG [ORKAMBI]	-	-
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	-	-
44119057	OMOP1113688	ivacaftor 125 MG / lumacaftor 200 MG [Orkamb]	-	-
46275585	1655930	ivacaftor 125 MG / lumacaftor 200 MG [ORKAMBI]	-	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
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	-	-
35200184	2053518	ivacaftor 188 MG / lumacaftor 150 MG [ORKAMBI]	-	-
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	-	-
1525625	2611459	ivacaftor 94 MG / lumacaftor 75 MG [ORKAMBI]	-	-
1525624	2611458	ivacaftor 94 MG / lumacaftor 75 MG Oral Granules	-	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
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				
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	-	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
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				
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]	-	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
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	-	-

Supportive CF therapies

Bile acid preparation (ursodeoxycholic acid)

Concept id	Concept Code	Concept Name	Descendants	Exclude
Bile acid preparation (ursodeoxycholic acid)				
21600513	A05AA02	ursodeoxycholic acid; oral	Yes	-
Mucolytics				
40254176	R05CB16	mannitol; inhalant	Yes	-
21603392	R05CB13	dornase alfa (desoxyribonuclease); inhalant	Yes	-
21603385	R05CB06	ambroxol; oral	Yes	-
21603380	R05CB01	acetylcysteine; inhalant, oral	Yes	-
Selective beta-2-adrenoreceptor agonists (salbutamol)				
21603256	R03AC02	salbutamol; inhalant	Yes	-
Aminoglycoside antibacterials (tobramycin)				
21602995	J01GB01	tobramycin; inhalant, parenteral	Yes	-
Proton pump inhibitors				
779984	2604577	vonoprazan	Yes	-
2100528	OMOP4976878	tegoprazan	Yes	-
911735	114979	rabeprazole	Yes	-
948078	40790	pantoprazole	Yes	-
923645	7646	omeprazole	Yes	-
929887	17128	lansoprazole	Yes	-
43009052	OMOP4700478	ilaprazole	Yes	-
36855962	OMOP5173579	FEXUPRAZAN	Yes	-
904453	283742	esomeprazole	Yes	-
36852858	OMOP5170474	DEXRABEPRAZOLE	Yes	-
19039926	816346	dexlansoprazole	Yes	-

Pancreatic enzymes

Concept id	Code	Name	Descendants	Exclude
41450326	OMOP2648288	1120 MG Pancreatin 18.4 UNT/MG Oral Solution [Kreon] Box of 200 by Mylan	-	-
41450334	OMOP2648296	1120 MG Pancreatin 18.4 UNT/MG Oral Solution [Kreon] Box of 300 by Mylan	-	-
41450367	OMOP2648329	1120 MG Pancreatin 18.4 UNT/MG Oral Solution [Kreon] Box of 50 by Mylan	-	-
41450370	OMOP2648332	1120 MG Pancreatin 18.4 UNT/MG Oral Solution [Kreon] Box of 900 by Mylan	-	-
41485322	OMOP2683284	20000 MG Pancreatin 0.25 UNT/MG Oral Granules [Kreon] Box of 1 by Mylan	-	-
41485929	OMOP2683891	20000 MG Pancreatin 0.25 UNT/MG Oral Granules [Kreon] Box of 5 by Mylan	-	-
37594165	OMOP4783591	20000 MG Pancreatin 52.2 UNT/MG Oral Tablet [Pancrin] by Mylan	-	-
43044879	OMOP4859883	20000 MG Sus scrofa pancreas preparation 0.00508 MG/MG Oral Granules [EUROBIOL] by Mayoly Spindler	-	-
41465665	OMOP2663627	2500 MG Pancreatin 8.32 UNT/MG Oral Solution [Kreon] Box of 20 by Mylan	-	-
41465786	OMOP2663748	2500 MG Pancreatin 8.32 UNT/MG Oral Solution [Kreon] Box of 200 by Mylan	-	-
41465535	OMOP2663497	2500 MG Pancreatin 8.32 UNT/MG Oral Solution [Kreon] Box of 50 by Mylan	-	-
41465905	OMOP2663867	2500 MG Pancreatin 8.32 UNT/MG Oral Solution [Kreon] Box of 900 by Mylan	-	-
41489815	OMOP2687777	25000 MG Pancreatin 1.6 UNT/MG Oral Powder [Pankreon] Box of 1 by Mylan	-	-
41466568	OMOP2664530	2990 MG Pancreatin 12 UNT/MG Oral Solution [Pankreon] Box of 20 by Mylan	-	-
41466888	OMOP2664850	2990 MG Pancreatin 12 UNT/MG Oral Solution [Pankreon] Box of 200 by Mylan	-	-
41466836	OMOP2664798	2990 MG Pancreatin 12 UNT/MG Oral Solution [Pankreon] Box of 300 by Mylan	-	-
41466388	OMOP2664350	2990 MG Pancreatin 12 UNT/MG Oral Solution [Pankreon] Box of 50 by Mylan	-	-
41440414	OMOP2638376	500 MG Pancreatin 41.6 UNT/MG Oral Solution [Kreon] Box of 200 by Mylan	-	-
41440459	OMOP2638421	500 MG Pancreatin 41.6 UNT/MG Oral Solution [Kreon] Box of 300 by Mylan	-	-
41440479	OMOP2638441	500 MG Pancreatin 41.6 UNT/MG Oral Solution [Kreon] Box of 50 by Mylan	-	-
41440389	OMOP2638351	500 MG Pancreatin 41.6 UNT/MG Oral Solution [Kreon] Box of 900 by Mylan	-	-
44208618	OMOP3085341	50000 MG Pancreatin 0.426 MG/MG Oral Powder [Pankreon] Box of 10	-	-

Concept id	Code	Name	Descendants	Exclude
41501222	OMOP2699184	50000 MG Pancreatin 0.8 UNT/MG Oral Powder [Pankreon] Box of 1 by Mylan	-	-
41521098	OMOP2719060	500000 MG Pancreatin 0.072 UNT/MG Oral Granules [Pankreon] Box of 1 by Mylan	-	-
41444696	OMOP2642658	689 MG Pancreatin 52.2 UNT/MG Oral Solution [Pankreon] Box of 200 by Mylan	-	-
44201039	OMOP3077762	689 MG Pancreatin 52.2 UNT/MG Oral Solution [Pankreon] Box of 300 by Mylan	-	-
41444704	OMOP2642666	689 MG Pancreatin 52.2 UNT/MG Oral Solution [Pankreon] Box of 50 by Mylan	-	-
19115053	560	alpha-amylase	-	-
43515558	OMOP2802673	alpha-amylase 22500 UNT / Lipase 25000 UNT / Protease 1250 UNT Delayed Release Oral Capsule	-	-
42900364	1306125	alpha-amylase A type 1-2	-	-
21109775	OMOP287495	ALPHA-D-GALACTOSIDASE ENZYME / Amylases / CELLULASE / Lactase / Lipase / Protease Oral Capsule [Digestizyme]	-	-
919204	743	amylase	-	-
40014010	437708	amylase Chewable Tablet	-	-
21119512	OMOP287525	Amylases / Betaine / Bromelains / Lipase Oral Tablet [Quest Enzyme Digest]	-	-
1396567	2171590	amylose, tapioca	-	-
41176694	OMOP2374656	Artemisia absinthium extract / Gonolobus Cundurango / Pancreatin Oral Tablet [Pascopankreat]	-	-
41111798	OMOP2309760	Aspergillus flavus var. oryzae / Bile Salts / Pancreatin Oral Tablet	-	-
40833257	OMOP2031219	Aspergillus flavus var. oryzae / Bile Salts / Pancreatin Oral Tablet [Combizym]	-	-
40957880	OMOP2155842	Aspergillus flavus var. oryzae / Bile Salts / Pancreatin Oral Tablet [Trizymal]	-	-
40833256	OMOP2031218	Aspergillus flavus var. oryzae / Pancreatin Oral Tablet [Combizym]	-	-
41138070	OMOP2336032	Aspergillus flavus var. oryzae 120 MG / Bile Salts 60 MG / Pancreatin 400 MG Oral Tablet [Combizym] Box of 100 by Daiichi Sankyo	-	-
41075212	OMOP2273174	Aspergillus flavus var. oryzae 120 MG / Pancreatin 212 MG Oral Tablet [Combizym] Box of 100 by Kohlpharma	-	-
41138069	OMOP2336031	Aspergillus flavus var. oryzae 120 MG / Pancreatin 212 MG Oral Tablet [Combizym] Box of 50 by Kohlpharma	-	-
41114020	OMOP2311982	Betaine / Pancreatin / Papain Oral Tablet [Unexym]	-	-
41051260	OMOP2249222	Betaine / Pancreatin Oral Tablet [Unexym]	-	-
41113995	OMOP2311957	Bile Salts / Pancreatin / Pepsin A Oral Tablet [Bilipeptal]	-	-
41145583	OMOP2343545	Bile Salts / Pancreatin / Pepsin A Oral Tablet [Helopanzym]	-	-
41208073	OMOP2406035	Bile Salts / Pancreatin Oral Tablet [Pankreatan]	-	-

Concept id	Code	Name	Descendants	Exclude
40957770	OMOP2155732	Bile Salts / Pancreatin Oral Tablet [Pankreon]	-	-
40833032	OMOP2030994	Calcium / Pancreatin Injectable Solution [Carzodelan]	-	-
986515	2219	cellulase	-	-
41269741	OMOP2467703	CELLULASE / Lipase / Pancreatin Oral Tablet [Stacho]	-	-
35198071	OMOP4819436	cellulase ap3	-	-
40988622	OMOP2186584	Curcuma longa whole extract / Pancreatin / Papain Oral Tablet [Chol Arbuz]	-	-
41269536	OMOP2467498	Curcuma longa whole extract / Pancreatin / Sodium Oral Tablet [Ventracid A]	-	-
41292559	OMOP2490521	Curcuma longa whole extract 105 MG / Pancreatin 37.4 MG Oral Tablet [Chol Arbuz] Box of 100 by Bittermedizin	-	-
41105601	OMOP2303563	Curcuma longa whole extract 105 MG / Pancreatin 37.4 MG Oral Tablet [Chol Arbuz] Box of 50 by Bittermedizin	-	-
41137020	OMOP2334982	Curcuma longa whole extract 5 MG / haronga leaf extract 5 MG / Pancreatin 150 MG Oral Tablet [Enzym Harongan] Box of 100 by Schwaben-Apotheke Herbert Aich	-	-
41042829	OMOP2240791	Curcuma longa whole extract 5 MG / haronga leaf extract 5 MG / Pancreatin 150 MG Oral Tablet [Enzym Harongan] Box of 50 by Schwaben-Apotheke Herbert Aich	-	-
40988621	OMOP2186583	Curcuma xanthorrhiza oil / Pancreatin / silybum marianum seed oil Oral Tablet [Enzym Hepaduran]	-	-
40832710	OMOP2030672	Curcumin / dimethicone / Pancreatin Oral Tablet [Digest Merz]	-	-
40988599	OMOP2186561	Cynara scolymus leaf extract / dimethicone / Pancreatin Oral Tablet [Carminagal]	-	-
35198203	OMOP4819568	digestive enzyme derived from aspergillus	-	-
41238473	OMOP2436435	dimethicone / methixene / Pancreatin Oral Tablet [Spasmo Canulase N]	-	-
41048819	OMOP2246781	dimethicone / Pancreatin / TRYPSIN Oral Tablet	-	-
41300420	OMOP2498382	dimethicone / Pancreatin Oral Solution [Pankreoflat]	-	-
41143066	OMOP2341028	dimethicone / Pancreatin Oral Tablet	-	-
41145039	OMOP2343001	dimethicone / Pancreatin Oral Tablet [Pankreoflat]	-	-
41011447	OMOP2209409	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Beragena	-	-
41230393	OMOP2428355	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Bestphago	-	-
41011448	OMOP2209410	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Emra-Med	-	-
41167927	OMOP2365889	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Eurim-Pharm	-	-
40949115	OMOP2147077	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Gppl	-	-

Concept id	Code	Name	Descendants	Exclude
41073856	OMOP2271818	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Medphano	-	-
40886881	OMOP2084843	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 100 by Opti	-	-
40886882	OMOP2084844	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Aca Mueller	-	-
41230394	OMOP2428356	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Beragena	-	-
41136714	OMOP2334676	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Bestphago	-	-
41167928	OMOP2365890	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Emra-Med	-	-
40855533	OMOP2053495	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Eurim-Pharm	-	-
40980120	OMOP2178082	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Gppl	-	-
40917770	OMOP2115732	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Medphano	-	-
41011449	OMOP2209411	dimethicone 80 MG / Pancreatin 170 MG Oral Tablet [Pankreoflat] Box of 50 by Opti	-	-
40957131	OMOP2155093	Escherichia coli / Pancreatin Oral Tablet [Enterotropin]	-	-
41081151	OMOP2279113	Lactase / Protease Oral Capsule [Sanalact Pro Laves]	-	-
990760	6406	lipase	-	-
35198031	OMOP4819396	lipase ap12	-	-
963982	1999473	liprotamase protease	-	-
40925281	OMOP2123243	Metoclopramide / Pancreatin Oral Tablet [Paspertase]	-	-
40915833	OMOP2113795	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Aca Mueller	-	-
41197402	OMOP2395364	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Beragena	-	-
41103334	OMOP2301296	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Emra-Med	-	-
40915831	OMOP2113793	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Kohlpharma	-	-
41040638	OMOP2238600	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Mtk	-	-
41290377	OMOP2488339	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 100 by Servopharma	-	-
40947228	OMOP2145190	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 20 by Mylan	-	-
41197401	OMOP2395363	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Aca Mueller	-	-
41321684	OMOP2519646	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Beragena	-	-

Concept id	Code	Name	Descendants	Exclude
41071908	OMOP2269870	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Emra-Med	-	-
41071907	OMOP2269869	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Kohlpharma	-	-
40947229	OMOP2145191	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Me	-	-
40947227	OMOP2145189	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Mtk	-	-
40853693	OMOP2051655	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Mylan	-	-
40915832	OMOP2113794	Metoclopramide 5 MG / Pancreatin 212 MG Oral Tablet [Paspertase] Box of 50 by Servopharma	-	-
21600701	A09AA02	multienzymes (lipase, protease etc.)	-	-
35197914	OMOP4819279	pancreatic digestive enzyme 8ap	-	-
35197994	OMOP4819359	pancreatic digestive enzyme ta	-	-
40894085	OMOP2092047	Pancreatin / Papain / Thymus Extracts Enema [Wobe Mugos]	-	-
40894084	OMOP2092046	Pancreatin / Simethicone Chewable Tablet [Enzym Lefax]	-	-
41081313	OMOP2279275	Pancreatin / Simethicone Oral Capsule [Fermento]	-	-
41112548	OMOP2310510	Pancreatin / Simethicone Oral Tablet [Meteozym]	-	-
44163385	OMOP3040108	Pancreatin 10000 UNT Delayed Release Oral Tablet [Helopan] Box of 50 by Nordmark	-	-
44182125	OMOP3058848	Pancreatin 10000 UNT Delayed Release Oral Tablet Box of 100 by Nordmark	-	-
44163377	OMOP3040100	Pancreatin 10000 UNT Delayed Release Oral Tablet Box of 50 by Novartis	-	-
44176985	OMOP3053708	Pancreatin 10000 UNT Oral Capsule [Cotazym] Box of 200	-	-
44182120	OMOP3058843	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 100 by Emra-Med	-	-
44178424	OMOP3055147	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 100 by Kohlpharma	-	-
44174647	OMOP3051370	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 100 by Mylan	-	-
44167179	OMOP3043902	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 1000 by Mylan	-	-
44170903	OMOP3047626	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 200 by Emra-Med	-	-
44159623	OMOP3036346	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 200 by Eurim-Pharm	-	-
44159622	OMOP3036345	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 200 by Kohlpharma	-	-
44174646	OMOP3051369	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 200 by Mylan	-	-
44178423	OMOP3055146	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 400 by Mylan	-	-

Concept id	Code	Name	Descendants	Exclude
44174648	OMOP3051371	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 50 by Emra-Med	-	-
44182121	OMOP3058844	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 50 by Mylan	-	-
44159621	OMOP3036344	Pancreatin 10000 UNT Oral Capsule [Kreon] Box of 500 by Mylan	-	-
44159620	OMOP3036343	Pancreatin 10000 UNT Oral Capsule [Pangrol] Box of 100 by Berlin-Chemie	-	-
44163379	OMOP3040102	Pancreatin 10000 UNT Oral Capsule [Pangrol] Box of 200 by Berlin-Chemie	-	-
44163380	OMOP3040103	Pancreatin 10000 UNT Oral Capsule [Pangrol] Box of 50 by Berlin-Chemie	-	-
44174645	OMOP3051368	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 100 by Glaxosmithkline	-	-
44159619	OMOP3036342	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 100 by Nordmark	-	-
44182119	OMOP3058842	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 200 by Glaxosmithkline	-	-
44185883	OMOP3062606	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 200 by Nordmark	-	-
44170902	OMOP3047625	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 50 by Glaxosmithkline	-	-
44170901	OMOP3047624	Pancreatin 10000 UNT Oral Capsule [Pankreatan] Box of 50 by Nordmark	-	-
36036820	OMOP5046819	pancreatin 10000 UNT Oral Capsule [Pankreatin Laves] Box of 100 by Laves	-	-
36036822	OMOP5046821	pancreatin 10000 UNT Oral Capsule [Pankreatin Laves] Box of 200 by Laves	-	-
36036818	OMOP5046817	pancreatin 10000 UNT Oral Capsule [Pankreatin Laves] Box of 50 by Laves	-	-
44185882	OMOP3062605	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 100 by Abbvie	-	-
44174644	OMOP3051367	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 100 by Allergan	-	-
44159618	OMOP3036341	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 100 by Axcan	-	-
44182118	OMOP3058841	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 20 by Abbvie	-	-
44182116	OMOP3058839	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 200 by Abbvie	-	-
44178421	OMOP3055144	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 200 by Allergan	-	-
44178420	OMOP3055143	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 200 by Axcan	-	-
44178422	OMOP3055145	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 50 by Abbvie	-	-

Concept id	Code	Name	Descendants	Exclude
44182117	OMOP3058840	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 50 by Allergan	-	-
44163378	OMOP3040101	Pancreatin 10000 UNT Oral Capsule [Panzytrat] Box of 50 by Axcan	-	-
40946361	OMOP2144323	Pancreatin 10000 UNT Oral Capsule [Unexym] Box of 100 by Repha	-	-
41196491	OMOP2394453	Pancreatin 10000 UNT Oral Capsule [Unexym] Box of 200 by Repha	-	-
44163381	OMOP3040104	Pancreatin 10000 UNT Oral Capsule Box of 100 by Laves	-	-
44182122	OMOP3058845	Pancreatin 10000 UNT Oral Capsule Box of 200 by Laves	-	-
44163382	OMOP3040105	Pancreatin 10000 UNT Oral Capsule Box of 50 by Laves	-	-
44159624	OMOP3036347	Pancreatin 10000 UNT Oral Tablet [Euflat] Box of 100 by Suedmedica	-	-
44185886	OMOP3062609	Pancreatin 10000 UNT Oral Tablet [Euflat] Box of 20 by Suedmedica	-	-
44174651	OMOP3051374	Pancreatin 10000 UNT Oral Tablet [Euflat] Box of 50 by Suedmedica	-	-
44174643	OMOP3051366	Pancreatin 10000 UNT Oral Tablet [Helopan] Box of 100 by Nordmark	-	-
44167181	OMOP3043904	Pancreatin 10000 UNT Oral Tablet [Mezym] Box of 100 by Berlin-Chemie	-	-
44174650	OMOP3051373	Pancreatin 10000 UNT Oral Tablet [Mezym] Box of 20 by Berlin-Chemie	-	-
44174649	OMOP3051372	Pancreatin 10000 UNT Oral Tablet [Mezym] Box of 50 by Berlin-Chemie	-	-
44170905	OMOP3047628	Pancreatin 10000 UNT Oral Tablet [Pankreatan] Box of 100 by Glaxosmithkline	-	-
44167180	OMOP3043903	Pancreatin 10000 UNT Oral Tablet [Pankreatan] Box of 20 by Glaxosmithkline	-	-
44170904	OMOP3047627	Pancreatin 10000 UNT Oral Tablet [Pankreatan] Box of 200 by Glaxosmithkline	-	-
44185885	OMOP3062608	Pancreatin 10000 UNT Oral Tablet [Pankreatan] Box of 50 by Glaxosmithkline	-	-
40915015	OMOP2112977	Pancreatin 10000 UNT Oral Tablet [Pankreon] Box of 100 by Mylan	-	-
41289506	OMOP2487468	Pancreatin 10000 UNT Oral Tablet [Pankreon] Box of 20 by Mylan	-	-
40915014	OMOP2112976	Pancreatin 10000 UNT Oral Tablet [Pankreon] Box of 200 by Mylan	-	-
40915016	OMOP2112978	Pancreatin 10000 UNT Oral Tablet [Pankreon] Box of 50 by Mylan	-	-
44185884	OMOP3062607	Pancreatin 10000 UNT Oral Tablet [Panpeptal] Box of 100 by Mibe	-	-
44182123	OMOP3058846	Pancreatin 10000 UNT Oral Tablet [Panpeptal] Box of 100 by Riemser	-	-

Concept id	Code	Name	Descendants	Exclude
44163384	OMOP3040107	Pancreatin 10000 UNT Oral Tablet [Panpeptal] Box of 50 by Mibe	-	-
44182124	OMOP3058847	Pancreatin 10000 UNT Oral Tablet Box of 100 by Novartis	-	-
41196484	OMOP2394446	Pancreatin 10200 UNT Oral Tablet [Unexym] Box of 100 by Repha	-	-
41102482	OMOP2300444	Pancreatin 10200 UNT Oral Tablet [Unexym] Box of 200 by Repha	-	-
44163376	OMOP3040099	Pancreatin 10200 UNT Oral Tablet [Unexym] Box of 50 by Repha	-	-
44170909	OMOP3047632	Pancreatin 13000 UNT Oral Capsule [Lipazym] Box of 200 by Bittermedizin	-	-
41147214	OMOP2345176	Pancreatin 1400 MG Oral Tablet Box of 100	-	-
40946365	OMOP2144327	Pancreatin 150 MG Delayed Release Oral Capsule [Kreon] Box of 100 by Cc	-	-
44163386	OMOP3040109	Pancreatin 150 MG Delayed Release Oral Capsule [Ozym] Box of 200 by Trommsdorff	-	-
36884741	OMOP998304	Pancreatin 150 MG Extended Release Oral Tablet	-	-
44178425	OMOP3055148	Pancreatin 150 MG Oral Capsule [Creon] Box of 200 by Axicorp	-	-
41071087	OMOP2269049	Pancreatin 150 MG Oral Capsule [Creon] Box of 50 by Axicorp	-	-
41289510	OMOP2487472	Pancreatin 150 MG Oral Capsule [Kreon] Box of 100 by Cc	-	-
44167183	OMOP3043906	Pancreatin 150 MG Oral Capsule [Kreon] Box of 100 by Eurim-Pharm	-	-
44182127	OMOP3058850	Pancreatin 150 MG Oral Capsule [Kreon] Box of 100 by Mylan	-	-
44163387	OMOP3040110	Pancreatin 150 MG Oral Capsule [Kreon] Box of 20 by Mylan	-	-
44170907	OMOP3047630	Pancreatin 150 MG Oral Capsule [Kreon] Box of 200 by Cc	-	-
44182128	OMOP3058851	Pancreatin 150 MG Oral Capsule [Kreon] Box of 50 by Cc	-	-
41071086	OMOP2269048	Pancreatin 150 MG Oral Capsule [Kreon] Box of 50 by Eurim-Pharm	-	-
44167182	OMOP3043905	Pancreatin 150 MG Oral Capsule [Kreon] Box of 50 by Mylan	-	-
44182126	OMOP3058849	Pancreatin 150 MG Oral Capsule [Ozym] Box of 100 by Trommsdorff	-	-
40915018	OMOP2112980	Pancreatin 150 MG Oral Capsule [Ozym] Box of 50 by Trommsdorff	-	-
40946369	OMOP2144331	Pancreatin 150 MG Oral Tablet [Mezym] Box of 40 by Berlin-Chemie	-	-
41154433	OMOP2352395	Pancreatin 154 MG Oral Capsule [Cotazym] Box of 100	-	-
40997961	OMOP2195923	Pancreatin 154 MG Oral Capsule [Cotazym] Box of 20	-	-
41185502	OMOP2383464	Pancreatin 154 MG Oral Capsule [Cotazym] Box of 50	-	-
40884085	OMOP2082047	Pancreatin 16000 UNT Oral Tablet [Pangrol] Box of 96 by Berlin-Chemie	-	-

Concept id	Code	Name	Descendants	Exclude
44167178	OMOP3043901	Pancreatin 196 MG Oral Capsule [Pankreatin Stada] Box of 100 by Aliud	-	-
44174642	OMOP3051365	Pancreatin 196 MG Oral Capsule [Pankreatin Stada] Box of 200 by Aliud	-	-
44170900	OMOP3047623	Pancreatin 196 MG Oral Capsule [Pankreatin Stada] Box of 50 by Aliud	-	-
44159616	OMOP3036339	Pancreatin 196 MG Oral Capsule Box of 100 by Ratiopharm	-	-
44159617	OMOP3036340	Pancreatin 196 MG Oral Capsule Box of 50 by Ratiopharm	-	-
40915011	OMOP2112973	Pancreatin 200 MG / Simethicone 21 MG Oral Capsule [Fermento] Box of 50 by Hommel	-	-
1972436	OMOP5165003	pancreatin 200 MG Oral Capsule [Pankreatin] Box of 100	-	-
40990668	OMOP2188630	Pancreatin 20000 UNT Delayed Release Oral Capsule	-	-
44174668	OMOP3051391	Pancreatin 20000 UNT Delayed Release Oral Capsule [Enzym Lefax] Box of 50 by Bayer	-	-
44170921	OMOP3047644	Pancreatin 20000 UNT Delayed Release Oral Tablet [Pankreatin Ratiopharm] Box of 50 by Ratiopharm		-
44182138	OMOP3058861	Pancreatin 20000 UNT Delayed Release Oral Tablet [Pankreatin Stada] Box of 50 by Stada	-	-
44159633	OMOP3036356	Pancreatin 20000 UNT Delayed Release Oral Tablet Box of 100 by Gastropharm	-	-
40959442	OMOP2157404	Pancreatin 20000 UNT Oral Capsule	-	-
44185898	OMOP3062621	Pancreatin 20000 UNT Oral Capsule [Cholspasminase] Box of 100 by Mylan	-	-
44170922	OMOP3047645	Pancreatin 20000 UNT Oral Capsule [Cholspasminase] Box of 50 by Mylan	-	-
44159634	OMOP3036357	Pancreatin 20000 UNT Oral Capsule [Cotazym] Box of 100 by Cheplapharm	-	-
44165707	OMOP3042430	Pancreatin 20000 UNT Oral Capsule [Cotazym] Box of 200	-	-
44182139	OMOP3058862	Pancreatin 20000 UNT Oral Capsule [Cotazym] Box of 200 by Cheplapharm	-	-
44174667	OMOP3051390	Pancreatin 20000 UNT Oral Capsule [Enzym Lefax] Box of 100 by Bayer	-	-
44167191	OMOP3043914	Pancreatin 20000 UNT Oral Capsule [Enzym Lefax] Box of 200 by Bayer	-	-
42875672	OMOP4872785	Pancreatin 20000 UNT Oral Capsule [Pankreatan] Box of 100 by Nordmark	-	-
42875674	OMOP4872787	Pancreatin 20000 UNT Oral Capsule [Pankreatan] Box of 200 by Nordmark	-	-
42875670	OMOP4872783	Pancreatin 20000 UNT Oral Capsule [Pankreatan] Box of 50 by Nordmark	-	-
44178434	OMOP3055157	Pancreatin 20000 UNT Oral Capsule [Panzytrat] Box of 100 by Abbvie	-	-
44174669	OMOP3051392	Pancreatin 20000 UNT Oral Capsule Box of 100 by Laves	-	-

Concept id	Code	Name	Descendants	Exclude
44185899	OMOP3062622	Pancreatin 20000 UNT Oral Capsule Box of 100 by Ratiopharm	-	-
44159635	OMOP3036358	Pancreatin 20000 UNT Oral Capsule Box of 100 by Stada	-	-
44170923	OMOP3047646	Pancreatin 20000 UNT Oral Capsule Box of 200 by Laves	-	-
44163402	OMOP3040125	Pancreatin 20000 UNT Oral Capsule Box of 200 by Ratiopharm	-	-
44178435	OMOP3055158	Pancreatin 20000 UNT Oral Capsule Box of 200 by Stada	-	-
44167194	OMOP3043917	Pancreatin 20000 UNT Oral Capsule Box of 50 by Laves	-	-
44167193	OMOP3043916	Pancreatin 20000 UNT Oral Capsule Box of 50 by Ratiopharm	-	-
44167192	OMOP3043915	Pancreatin 20000 UNT Oral Capsule Box of 50 by Stada	-	-
40990669	OMOP2188631	Pancreatin 20000 UNT Oral Tablet	-	-
44159636	OMOP3036359	Pancreatin 20000 UNT Oral Tablet [Cholspasminase] Box of 100 by Mylan	-	-
44178439	OMOP3055162	Pancreatin 20000 UNT Oral Tablet [Cholspasminase] Box of 20 by Mylan	-	-
44178438	OMOP3055161	Pancreatin 20000 UNT Oral Tablet [Cholspasminase] Box of 50 by Mylan	-	-
44178437	OMOP3055160	Pancreatin 20000 UNT Oral Tablet [Enzymed] Box of 30 by Medice	-	-
44170925	OMOP3047648	Pancreatin 20000 UNT Oral Tablet [Hevertozym] Box of 100 by Hevert	-	-
44170926	OMOP3047649	Pancreatin 20000 UNT Oral Tablet [Hevertozym] Box of 50 by Hevert	-	-
44165708	OMOP3042431	Pancreatin 20000 UNT Oral Tablet [Nutrizym] Box of 100	-	-
44180694	OMOP3057417	Pancreatin 20000 UNT Oral Tablet [Nutrizym] Box of 20	-	-
44169499	OMOP3046222	Pancreatin 20000 UNT Oral Tablet [Nutrizym] Box of 50	-	-
44174671	OMOP3051394	Pancreatin 20000 UNT Oral Tablet [Pangrol] Box of 100 by Berlin-Chemie	-	-
44163404	OMOP3040127	Pancreatin 20000 UNT Oral Tablet [Pangrol] Box of 200 by Berlin-Chemie	-	-
44174672	OMOP3051395	Pancreatin 20000 UNT Oral Tablet [Pangrol] Box of 50 by Berlin-Chemie	-	-
41258423	OMOP2456385	Pancreatin 20000 UNT Oral Tablet [Pankreatin Ratiopharm] Box of 100 by Ratiopharm	-	-
41039801	OMOP2237763	Pancreatin 20000 UNT Oral Tablet [Pankreatin Ratiopharm] Box of 20 by Ratiopharm	-	-
44167190	OMOP3043913	Pancreatin 20000 UNT Oral Tablet [Pankreatin Stada] Box of 100 by Stada	-	-
44178436	OMOP3055159	Pancreatin 20000 UNT Oral Tablet [Pankreatin Stada] Box of 20 by Stada	-	-
44167195	OMOP3043918	Pancreatin 20000 UNT Oral Tablet [Panzynorm Ft] Box of 100 by Abbvie	-	-

Concept id	Code	Name	Descendants	Exclude
44174670	OMOP3051393	Pancreatin 20000 UNT Oral Tablet [Panzynorm Ft] Box of 100 by Allergan	-	-
44163403	OMOP3040126	Pancreatin 20000 UNT Oral Tablet [Panzynorm Ft] Box of 50 by Abbvie	-	-
44185900	OMOP3062623	Pancreatin 20000 UNT Oral Tablet [Panzynorm Ft] Box of 50 by Allergan	-	-
40946371	OMOP2144333	Pancreatin 20000 UNT Oral Tablet [Panzytrat] Box of 1 by Allergan	-	-
40884089	OMOP2082051	Pancreatin 20000 UNT Oral Tablet [Panzytrat] Box of 1 by Axcan	-	-
40928116	OMOP2126078	Pancreatin 20000 UNT Oral Tablet Box of 100	-	-
40959443	OMOP2157405	Pancreatin 20000 UNT Oral Tablet Box of 200	-	-
44170927	OMOP3047650	Pancreatin 20000 UNT Oral Tablet Box of 200 by Laves	-	-
44185902	OMOP3062625	Pancreatin 20000 UNT Oral Tablet Box of 200 by Stada	-	-
44159637	OMOP3036360	Pancreatin 20000 UNT Oral Tablet Box of 25 by Laves	-	-
41209691	OMOP2407653	Pancreatin 20000 UNT Oral Tablet Box of 50	-	-
44174666	OMOP3051389	Pancreatin 20000 UNT Oral Tablet Box of 50 by Gastropharm	-	-
44184399	OMOP3061122	Pancreatin 250 MG Delayed Release Oral Tablet [Meteophyt] Box of 100	-	-
44180674	OMOP3057397	Pancreatin 250 MG Delayed Release Oral Tablet [Meteophyt] Box of 50	-	-
40884075	OMOP2082037	Pancreatin 250 MG Delayed Release Oral Tablet [Pankreatin Opt] Box of 100 by Optimed	-	-
44163375	OMOP3040098	Pancreatin 250 MG Oral Tablet [Bilipeptal] Box of 100 by Evisco	-	-
44170898	OMOP3047621	Pancreatin 250 MG Oral Tablet [Bilipeptal] Box of 50 by Evisco	-	-
41102481	OMOP2300443	Pancreatin 250 MG Oral Tablet [Pancholtruw N] Box of 50 by TRUW	-	-
41320822	OMOP2518784	Pancreatin 250 MG Oral Tablet Box of 100 by Laves	-	-
44174641	OMOP3051364	Pancreatin 250 MG Oral Tablet Box of 50 by Laves	-	-
44182131	OMOP3058854	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 100 by Eurim-Pharm	-	-
44174659	OMOP3051382	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 100 by Mylan	-	-
44163396	OMOP3040119	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 1000 by Mylan	-	-
44185893	OMOP3062616	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 20 by Mylan	-	-
44185891	OMOP3062614	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 200 by Emra-Med	-	-
44159629	OMOP3036352	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 200 by Eurim-Pharm	-	-

Concept id	Code	Name	Descendants	Exclude
44185890	OMOP3062613	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 200 by Gerke	-	-
44170915	OMOP3047638	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 200 by Mylan	-	-
44170914	OMOP3047637	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 250 by Mylan	-	-
44167187	OMOP3043910	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 400 by Mylan	-	-
44185892	OMOP3062615	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 50 by Eurim-Pharm	-	-
44163397	OMOP3040120	Pancreatin 25000 UNT Oral Capsule [Kreon] Box of 50 by Mylan	-	-
44163395	OMOP3040118	Pancreatin 25000 UNT Oral Capsule [Pancrin] Box of 200 by Mylan	-	-
44178427	OMOP3055150	Pancreatin 25000 UNT Oral Capsule [Pangrol] Box of 100 by Berlin-Chemie	-	-
44182130	OMOP3058853	Pancreatin 25000 UNT Oral Capsule [Pangrol] Box of 20 by Berlin-Chemie	-	-
44185889	OMOP3062612	Pancreatin 25000 UNT Oral Capsule [Pangrol] Box of 200 by Berlin-Chemie	-	-
44178428	OMOP3055151	Pancreatin 25000 UNT Oral Capsule [Pangrol] Box of 50 by Berlin-Chemie	-	-
44178426	OMOP3055149	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 100 by Glaxosmithkline	-	-
44159628	OMOP3036351	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 100 by Nordmark	-	-
44170912	OMOP3047635	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 200 by Glaxosmithkline	-	-
44163393	OMOP3040116	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 200 by Nordmark	-	-
44170913	OMOP3047636	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 50 by Glaxosmithkline	-	-
44163394	OMOP3040117	Pancreatin 25000 UNT Oral Capsule [Pankreatan] Box of 50 by Nordmark	-	-
44174656	OMOP3051379	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 100 by Abbvie	-	-
44167185	OMOP3043908	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 100 by Allergan	-	-
44170911	OMOP3047634	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 100 by Axcan	-	-
44163392	OMOP3040115	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 1000 by Axcan	-	-
44174655	OMOP3051378	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 200 by Abbvie	-	-
44170910	OMOP3047633	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 200 by Allergan	-	-

Concept id	Code	Name	Descendants	Exclude
44185888	OMOP3062611	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 200 by Axcan	-	-
44174658	OMOP3051381	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 50 by Abbvie	-	-
44167186	OMOP3043909	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 50 by Allergan	-	-
44174657	OMOP3051380	Pancreatin 25000 UNT Oral Capsule [Panzytrat] Box of 50 by Axcan	-	-
41196494	OMOP2394456	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Aca Mueller	-	-
41258405	OMOP2456367	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Beragena	-	-
40852825	OMOP2050787	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Emra-Med	-	-
40915017	OMOP2112979	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Eurim-Pharm	-	-
41008663	OMOP2206625	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Gppl	-	-
41008662	OMOP2206624	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Mtk	-	-
41133856	OMOP2331818	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Mylan	-	-
41071082	OMOP2269044	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 100 by Servopharma	-	-
41196493	OMOP2394455	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Aca Mueller	-	-
40884078	OMOP2082040	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Beragena	-	-
41102492	OMOP2300454	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Emra-Med	-	-
41165146	OMOP2363108	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Gppl	-	-
41039788	OMOP2237750	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Kohlpharma	-	-
40946363	OMOP2144325	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Mtk	-	-
41008661	OMOP2206623	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Mylan	-	-
41102491	OMOP2300453	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Opti	-	-
41102490	OMOP2300452	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 200 by Servopharma	-	-
41320829	OMOP2518791	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Aca Mueller	-	-
41071083	OMOP2269045	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Beragena	-	-

Concept id	Code	Name	Descendants	Exclude
41227586	OMOP2425548	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Emra-Med	-	-
40946364	OMOP2144326	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Gppl	-	-
41258406	OMOP2456368	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Mylan	-	-
41133854	OMOP2331816	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Opti	-	-
41102493	OMOP2300455	Pancreatin 28000 UNT Oral Tablet [Pankreon] Box of 50 by Servopharma	-	-
36886699	OMOP994396	Pancreatin 300 MG Extended Release Oral Tablet	-	-
44180691	OMOP3057414	Pancreatin 300 MG Oral Capsule [Cotazym] Box of 100	-	-
40935498	OMOP2133460	Pancreatin 300 MG Oral Capsule [Cotazym] Box of 20	-	-
40935497	OMOP2133459	Pancreatin 300 MG Oral Capsule [Cotazym] Box of 50	-	-
40822527	OMOP2020489	Pancreatin 300 MG Oral Capsule [Creon] Box of 100 by Axicorp	-	-
41196504	OMOP2394466	Pancreatin 300 MG Oral Capsule [Creon] Box of 200 by Axicorp	-	-
41102502	OMOP2300464	Pancreatin 300 MG Oral Capsule [Creon] Box of 50 by Axicorp	-	-
41029025	OMOP2226987	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100	-	-
41196503	OMOP2394465	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100 by Aca Mueller	-	-
40946368	OMOP2144330	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100 by Emra-Med	-	-
41227589	OMOP2425551	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100 by Gerke	-	-
41133858	OMOP2331820	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100 by Kohlpharma	-	-
41320834	OMOP2518796	Pancreatin 300 MG Oral Capsule [Kreon] Box of 100 by Orifarm Leverkus	-	-
41185525	OMOP2383487	Pancreatin 300 MG Oral Capsule [Kreon] Box of 200	-	-
41102501	OMOP2300463	Pancreatin 300 MG Oral Capsule [Kreon] Box of 200 by Aca Mueller	-	-
41039797	OMOP2237759	Pancreatin 300 MG Oral Capsule [Kreon] Box of 200 by Cc	-	-
41289514	OMOP2487476	Pancreatin 300 MG Oral Capsule [Kreon] Box of 200 by Kohlpharma	-	-
41039796	OMOP2237758	Pancreatin 300 MG Oral Capsule [Kreon] Box of 200 by Orifarm Leverkus	-	-
40915022	OMOP2112984	Pancreatin 300 MG Oral Capsule [Kreon] Box of 50 by Cc	-	-
41008670	OMOP2206632	Pancreatin 300 MG Oral Capsule [Kreon] Box of 50 by Gerke	-	-
41320832	OMOP2518794	Pancreatin 300 MG Oral Capsule [Lipazym] Box of 100 by Bittermedizin	-	-

Concept id	Code	Name	Descendants	Exclude
41289515	OMOP2487477	Pancreatin 300 MG Oral Capsule [Lipazym] Box of 1000 by Bittermedizin	-	-
41039798	OMOP2237760	Pancreatin 300 MG Oral Capsule [Lipazym] Box of 50 by Bittermedizin	-	-
41008666	OMOP2206628	Pancreatin 300 MG Oral Capsule [Lipazym] Box of 500 by Bittermedizin	-	-
41165152	OMOP2363114	Pancreatin 300 MG Oral Capsule [Ozym] Box of 100 by Trommsdorff	-	-
40977347	OMOP2175309	Pancreatin 300 MG Oral Capsule [Ozym] Box of 200 by Trommsdorff	-	-
41196505	OMOP2394467	Pancreatin 300 MG Oral Capsule [Ozym] Box of 50 by Trommsdorff	-	-
41289516	OMOP2487478	Pancreatin 300 MG Oral Capsule Box of 200 by Ratiopharm	-	-
44173228	OMOP3049951	Pancreatin 30000 UNT Oral Capsule [Cotazym] Box of 100	-	-
44170918	OMOP3047641	Pancreatin 30000 UNT Oral Capsule [Cotazym] Box of 100 by Cheplapharm	-	-
44161918	OMOP3038641	Pancreatin 30000 UNT Oral Capsule [Cotazym] Box of 200	-	-
44180689	OMOP3057412	Pancreatin 30000 UNT Oral Capsule [Cotazym] Box of 50	-	-
44174665	OMOP3051388	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 100 by Abbvie	-	-
44167189	OMOP3043912	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 100 by Allergan	-	-
44182137	OMOP3058860	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 100 by Axcan	-	-
44159632	OMOP3036355	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 20 by Abbvie	-	-
44170920	OMOP3047643	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 50 by Abbvie	-	-
44170919	OMOP3047642	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 50 by Allergan	-	-
44159631	OMOP3036354	Pancreatin 30000 UNT Oral Tablet [Panpur] Box of 50 by Axcan	-	-
41320830	OMOP2518792	Pancreatin 325 MG Oral Capsule [Digest Merz] Box of 50 by Merz	-	-
40884092	OMOP2082054	Pancreatin 325 MG Oral Capsule [Panzytrat] Box of 20 by Abbvie	-	-
40884091	OMOP2082053	Pancreatin 325 MG Oral Capsule [Panzytrat] Box of 50 by Abbvie	-	-
41258412	OMOP2456374	Pancreatin 325 MG Oral Tablet [Pankreatan] Box of 20 by Brunnengraeber	-	-
40946367	OMOP2144329	Pancreatin 325 MG Oral Tablet [Pankreatan] Box of 50 by Brunnengraeber	-	-
41258415	OMOP2456377	Pancreatin 3500 UNT Oral Tablet [Mezym] Box of 100 by Berlin-Chemie	-	-

Concept id	Code	Name	Descendants	Exclude
44161083	OMOP3037806	Pancreatin 36000 UNT Oral Capsule	-	-
1972441	OMOP5165008	pancreatin 36000 UNT Oral Capsule [Kreon] Box of 400 by Mylan	-	-
36036826	OMOP5046825	pancreatin 36000 UNT Oral Capsule [Kreon] Box of 50 by Mylan	-	-
44163390	OMOP3040113	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 100 by Glaxosmithkline	-	-
44163389	OMOP3040112	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 100 by Nordmark	-	-
44185887	OMOP3062610	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 200 by Glaxosmithkline	-	-
44163388	OMOP3040111	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 200 by Nordmark	-	-
44182129	OMOP3058852	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 50 by Glaxosmithkline	-	-
44163391	OMOP3040114	Pancreatin 36000 UNT Oral Capsule [Pankreatan] Box of 50 by Nordmark	-	-
44172443	OMOP3049166	Pancreatin 36000 UNT Oral Tablet	-	-
44174654	OMOP3051377	Pancreatin 36000 UNT Oral Tablet [Pankreatan] Box of 200 by Glaxosmithkline	-	-
43199548	OMOP483028	Pancreatin 400 MG Extended Release Oral Tablet [Creon] Box of 100 by Mylan	-	-
44188240	OMOP3064963	Pancreatin 40000 UNT Oral Capsule [Cotazym] Box of 100	-	-
44174664	OMOP3051387	Pancreatin 40000 UNT Oral Capsule [Cotazym] Box of 100 by Cheplapharm	-	-
44173226	OMOP3049949	Pancreatin 40000 UNT Oral Capsule [Cotazym] Box of 200	-	-
44163401	OMOP3040124	Pancreatin 40000 UNT Oral Capsule [Cotazym] Box of 200 by Cheplapharm	-	-
44173227	OMOP3049950	Pancreatin 40000 UNT Oral Capsule [Cotazym] Box of 50	-	-
44178433	OMOP3055156	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 100 by Cc	-	-
44182136	OMOP3058859	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 100 by Eurim-Pharm	-	-
44185897	OMOP3062620	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 100 by Mylan	-	-
44182135	OMOP3058858	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 200 by Cc	-	-
44178432	OMOP3055155	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 200 by Eurim-Pharm	-	-
44174662	OMOP3051385	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 200 by Mylan	-	-
44163400	OMOP3040123	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 400 by Mylan	-	-
44174663	OMOP3051386	Pancreatin 40000 UNT Oral Capsule [Kreon] Box of 50 by Mylan	-	-

Concept id	Code	Name	Descendants	Exclude
44159630	OMOP3036353	Pancreatin 40000 UNT Oral Capsule [Ozym] Box of 100 by Trommsdorff	-	-
44185895	OMOP3062618	Pancreatin 40000 UNT Oral Capsule [Ozym] Box of 200 by Trommsdorff	-	-
44185896	OMOP3062619	Pancreatin 40000 UNT Oral Capsule [Ozym] Box of 50 by Trommsdorff	-	-
40915024	OMOP2112986	Pancreatin 40000 UNT Oral Capsule [Pancrin] Box of 200 by Mylan	-	-
44159077	OMOP3035800	Pancreatin 40000 UNT Oral Capsule [Pangrol] Box of 100 by Berlin-Chemie	-	-
44163399	OMOP3040122	Pancreatin 40000 UNT Oral Capsule [Pangrol] Box of 200 by Berlin-Chemie	-	-
44163398	OMOP3040121	Pancreatin 40000 UNT Oral Capsule [Pangrol] Box of 300 by Berlin-Chemie	-	-
44185894	OMOP3062617	Pancreatin 40000 UNT Oral Capsule [Pangrol] Box of 50 by Berlin-Chemie	-	-
44182132	OMOP3058855	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 100 by Abbvie	-	-
44178430	OMOP3055153	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 100 by Allergan	-	-
44178429	OMOP3055152	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 100 by Axcan	-	-
44182134	OMOP3058857	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 20 by Abbvie	-	-
44174661	OMOP3051384	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 200 by Abbvie	-	-
44167188	OMOP3043911	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 200 by Allergan	-	-
44170916	OMOP3047639	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 200 by Axcan	-	-
44182133	OMOP3058856	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 50 by Abbvie	-	-
44178431	OMOP3055154	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 50 by Allergan	-	-
44170917	OMOP3047640	Pancreatin 40000 UNT Oral Capsule [Panzytrat] Box of 50 by Axcan	-	-
36505759	OMOP4835114	Pancreatin 40000 UNT Oral Capsule by Nordmark	-	-
41258416	OMOP2456378	Pancreatin 40000 UNT Oral Tablet [Kreon] Box of 100 by Mylan	-	-
41165155	OMOP2363117	Pancreatin 40000 UNT Oral Tablet [Kreon] Box of 200 by Mylan	-	-
41289519	OMOP2487481	Pancreatin 40000 UNT Oral Tablet [Kreon] Box of 50 by Mylan	-	-
41227582	OMOP2425544	Pancreatin 50 MG / Simethicone 40 MG Chewable Tablet [Enzym Lefax] Box of 100 by Bayer	-	-

Concept id	Code	Name	Descendants	Exclude
41039784	OMOP2237746	Pancreatin 50 MG / Simethicone 40 MG Chewable Tablet [Enzym Lefax] Box of 20 by Bayer	-	-
40977336	OMOP2175298	Pancreatin 50 MG / Simethicone 40 MG Chewable Tablet [Enzym Lefax] Box of 50 by Bayer	-	-
41289508	OMOP2487470	Pancreatin 500 MG Oral Capsule Box of 100 by Natur	-	-
44159626	OMOP3036349	Pancreatin 500 MG Oral Capsule Box of 50 by Natur	-	-
44167177	OMOP3043900	Pancreatin 5000 UNT Oral Tablet [Mineatin] Box of 60 by Biokirch	-	-
43029334	OMOP4844409	Pancreatin 60 MG Oral Granules	-	-
44174653	OMOP3051376	Pancreatin 600 MG Oral Tablet [Pankreatan] Box of 100 by Glaxosmithkline	-	-
44159625	OMOP3036348	Pancreatin 600 MG Oral Tablet [Pankreatan] Box of 20 by Glaxosmithkline	-	-
44170906	OMOP3047629	Pancreatin 600 MG Oral Tablet [Pankreatan] Box of 50 by Glaxosmithkline	-	-
41227583	OMOP2425545	Pancreatin 6000 UNT Oral Tablet [Festal] Box of 100 by M.C.M.Klosterfrau Vertriebs-Gmbh	-	-
40946358	OMOP2144320	Pancreatin 6000 UNT Oral Tablet [Festal] Box of 20 by M.C.M.Klosterfrau Vertriebs-Gmbh	-	-
41320821	OMOP2518783	Pancreatin 6000 UNT Oral Tablet [Festal] Box of 50 by M.C.M.Klosterfrau Vertriebs-Gmbh	-	-
41289522	OMOP2487484	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 100 by Kohlpharma	-	-
41008673	OMOP2206635	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 100 by Orifarm Leverkus	-	-
41165157	OMOP2363119	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 200 by Eurim-Pharm	-	-
40915026	OMOP2112988	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 50 by Eurim-Pharm	-	-
41102508	OMOP2300470	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 50 by Kohlpharma	-	-
40977351	OMOP2175313	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 50 by Mtk	-	-
41071097	OMOP2269059	Pancreatin 700 MG Oral Tablet [Pankreon] Box of 50 by Orifarm Leverkus	-	-
40915025	OMOP2112987	Pancreatin 700 MG Oral Tablet [Panpur] Box of 20 by Abbvie	-	-
41039791	OMOP2237753	Pancreatin 8000 UNT Oral Tablet [Cholspasminase] Box of 100 by Mylan	-	-
40852827	OMOP2050789	Pancreatin 8000 UNT Oral Tablet [Cholspasminase] Box of 20 by Mylan	-	-
40884079	OMOP2082041	Pancreatin 8000 UNT Oral Tablet [Pankreon] Box of 20 by Mylan	-	-
41196497	OMOP2394459	Pancreatin 8000 UNT Oral Tablet [Pankreon] Box of 50 by Mylan	-	-

Concept id	Code	Name	Descendants	Exclude
44159627	OMOP3036350	Pancreatin 840 MG Oral Tablet [Pankreatan] Box of 1000 by Brunnengraeber	-	-
44167184	OMOP3043907	Pancreatin 840 MG Oral Tablet [Pankreatan] Box of 40 by Brunnengraeber	-	-
44170908	OMOP3047631	Pancreatin 840 MG Oral Tablet [Pankreatan] Box of 50 by Brunnengraeber	-	-
41237548	OMOP2435510	Pancreatin Chewable Tablet [Enzym Lefax]	-	-
40925100	OMOP2123062	Pancreatin Delayed Release Oral Capsule [Lipazym]	-	-
40069734	373216	pancreatin Oral Capsule	-	-
40823877	OMOP2021839	Pancreatin Oral Capsule [Enzym Lefax]	-	-
43744480	OMOP880950	Pancreatin Oral Capsule [Lipazym]	-	-
40987599	OMOP2185561	Pancreatin Oral Capsule [Pancrin]	-	-
44183340	OMOP3060063	Pancreatin Oral Tablet [Helopanflat]	-	-
40925103	OMOP2123065	Pancreatin Oral Tablet [Panzynorm Ft]	-	-
43289395	OMOP541857	Pancrelipase Oral Capsule	-	-
931973	8031	protease	-	-
2100534	OMOP4976876	semi-alkaline protease	-	-
43037580	OMOP4852624	Sus scrofa pancreas preparation 170 MG Extended Release Oral Tablet [EUROBIOL] Box of 100 by Mayoly Spindler	-	-
43037563	OMOP4852608	Sus scrofa pancreas preparation 340 MG Extended Release Oral Tablet	-	-
43037570	OMOP4852614	Sus scrofa pancreas preparation 350 MG Extended Release Oral Tablet	-	-

List of concept definitions for conditions of interest

For incidence analyses of selected events of special interest, i.e., cataract, depression, and anxiety, individuals with a record from a list of prevalent concept ids for these outcomes, defined as those already present before the earliest record CF diagnosis during the study period, prior to the ID, were excluded (please refer to the “prevalent” column in the tables of these outcomes below).

Cataract

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
375545	194000000	Cataract	Yes	-	Yes
37108935	15700000000000000	Left after-cataract not obscuring vision	-	Yes	-
37108934	15700000000000000	Right after-cataract not obscuring vision	-	Yes	-
4259620	411000000	Anterior capsule opacification following extraction of cataract	-	Yes	-
36714335	720000000	Autosomal dominant optic atrophy and cataract	-	Yes	-
443569	416000000	Cataract associated with infrared radiation	-	Yes	-
377864	71044004	Cataract associated with radiation	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
381566	194000000	Cataract due to inflammatory disorder	-	Yes	-
36713529	718000000	Cataract due to pseudohypoparathyroidism	-	Yes	-
3656862	332000000000000	Cataract of right eye caused by corticosteroid	-	Yes	-
36684615	332000000000000	Cataract of right eye due to and following trauma	-	Yes	-
4225524	405000000	Corticosteroid induced cataract	-	Yes	-
4157030	370000000	Mittendorf dot	-	Yes	-
4048386	15552004	Osteogenesis imperfecta, recessive perinatal lethal, with microcephaly AND cataracts	-	Yes	-
380101	194000000	Partially resolved traumatic cataract	-	Yes	-
4102697	253000000	Rubella cataract	-	Yes	-
381279	68216000	Tetanic cataract	-	Yes	-
374642	8656007	Total traumatic cataract	-	Yes	-
376401	34361001	Traumatic cataract	-	Yes	-
4081144	247000000	Spontaneous reabsorption of cataract	-	Yes	-
37396330	716000000	Absence deformity of leg and congenital cataract syndrome	-	Yes	-
37310624	347000000000000	Bilateral congenital anterior subcapsular polar cataracts	-	Yes	-
36684791	347000000000000	Bilateral congenital cataract of eyes	-	Yes	-
3657068	347000000000000	Bilateral congenital combined form cataract of eyes	-	Yes	-
3657147	681000000000000	Bilateral congenital cortical cataract of eyes	-	Yes	-
37207996	347000000000000	Bilateral congenital nuclear cataracts of eyes	-	Yes	-
37207995	347000000000000	Bilateral congenital posterior subcapsular polar cataracts of eyes	-	Yes	-
3657086	349000000000000	Bilateral congenital zonular cataract	-	Yes	-
37111650	727000000	Cataract, congenital heart disease, neural tube defect syndrome	-	Yes	-
4100720	253000000	Congenital anterior polar cataract	-	Yes	-
45757718	343000000000000	Congenital anterior subcapsular polar cataract	-	Yes	-
37310640	341000000000000	Congenital anterior subcapsular polar cataract of left eye	-	Yes	-
37310630	336000000000000	Congenital anterior subcapsular polar cataract of right eye	-	Yes	-
4070185	204000000	Congenital blue dot cataract	-	Yes	-
443791	28550007	Congenital capsular cataract	-	Yes	-
380513	79410001	Congenital cataract	-	Yes	-
37116290	733000000	Congenital cataract ichthyosis syndrome	-	Yes	-
36684731	341000000000000	Congenital cataract of left eye	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
36684665	336000000000000	Congenital cataract of right eye	-	Yes	-
36714026	719000000	Congenital cataract with ataxia and deafness syndrome	-	Yes	-
36716387	722000000	Congenital cataract with deafness and hypogonadism syndrome	-	Yes	-
36716388	722000000	Congenital cataract with hypertrichosis and intellectual disability syndrome	-	Yes	-
36676682	774000000	Congenital cataract, hearing loss, severe developmental delay syndrome	-	Yes	-
36713473	718000000	Congenital cataract, hypertrophic cardiomyopathy, mitochondrial myopathy syndrome	-	Yes	-
36676498	773000000	Congenital cataract, progressive muscular hypotonia, hearing loss, developmental delay syndrome	-	Yes	-
45770920	343000000000000	Congenital combined form cataract	-	Yes	-
4280227	66499004	Congenital cortical cataract	-	Yes	-
3657138	680000000000000	Congenital cortical cataract of left eye	-	Yes	-
3657139	680000000000000	Congenital cortical cataract of right eye	-	Yes	-
4069800	204000000	Congenital lamellar cataract	-	Yes	-
4069803	204000000	Congenital membranous cataract	-	Yes	-
37395848	715000000	Congenital muscular dystrophy with infantile cataract and hypogonadism syndrome	-	Yes	-
3657007	341000000000000	Congenital nuclear cataract of left eye	-	Yes	-
3656920	336000000000000	Congenital nuclear cataract of right eye	-	Yes	-
4100889	253000000	Congenital polar cataract	-	Yes	-
4102696	253000000	Congenital posterior polar cataract	-	Yes	-
45757716	343000000000000	Congenital posterior subcapsular polar cataract	-	Yes	-
37207948	341000000000000	Congenital posterior subcapsular polar cataract of left eye	-	Yes	-
37207888	336000000000000	Congenital posterior subcapsular polar cataract of right eye	-	Yes	-
381392	76562003	Congenital subcapsular cataract	-	Yes	-
4099981	253000000	Congenital sutural cataract	-	Yes	-
4105600	29590001	Congenital total cataract	-	Yes	-
4068699	21590003	Congenital zonular cataract	-	Yes	-
1340287	OMOP5165942	Exacerbation of congenital cataract	-	Yes	-
36676675	774000000	Porencephaly, microcephaly, bilateral congenital cataract syndrome	-	Yes	-
36715121	721000000	Cardiomyopathy with cataract and hip spine disease syndrome	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
36717554	722000000	Cataract and microcornea syndrome	-	Yes	-
36713858	719000000	Cataract glaucoma syndrome	-	Yes	-
37395915	716000000	Cochleosaccular degeneration and cataract syndrome	-	Yes	-
36716390	722000000	Crome syndrome	-	Yes	-
36680594	778000000	Foveal hypoplasia with presenile cataract syndrome	-	Yes	-
36715372	721000000	Hydrocephalus with endocardial fibroelastosis and cataract syndrome	-	Yes	-
45765456	702000000	Hyperferritinemia cataract syndrome	-	Yes	-
36715527	721000000	Hypergonadotropic hypogonadism with cataract syndrome	-	Yes	-
36716124	722000000	Intellectual disability with cataract and kyphosis syndrome	-	Yes	-
37111654	727000000	Intellectual disability, cataract, calcified pinna, myopathy syndrome	-	Yes	-
36716448	722000000	Juvenile cataract, microcornea, renal glucosuria syndrome	-	Yes	-
37396247	716000000	Karandikar Maria Kamble syndrome	-	Yes	-
4216348	80734006	Marinesco-SjÃ¶gren syndrome	-	Yes	-
36716389	722000000	Martsolf syndrome	-	Yes	-
36675066	771000000	Microcornea, rod-cone dystrophy, cataract, posterior staphyloma syndrome	-	Yes	-
40482880	445000000	Nance-Horan syndrome	-	Yes	-
37396376	716000000	Nathalie syndrome	-	Yes	-
36715408	721000000	Siegler Brewer Carey syndrome	-	Yes	-
37117168	724000000	Spinal muscular atrophy, Dandy-Walker malformation, cataract syndrome	-	Yes	-
36713803	719000000	Spondyloepiphyseal dysplasia, craniosynostosis, cleft palate, cataract and intellectual disability syndrome	-	Yes	-
36675714	772000000	Warburg micro syndrome	-	Yes	-
37396246	716000000	Wellesley Carman French syndrome	-	Yes	-
434145	5361003	Embryonal nuclear cataract	-	Yes	-
441846	51044000	After-cataract not obscuring vision following extraction of cataract	-	Yes	-
37108936	15700000000000000	After-cataract of bilateral eyes	-	Yes	-
37309693	16000000000000000	After-cataract of left eye	-	Yes	-
37309694	16000000000000000	After-cataract of right eye	-	Yes	-
436118	194000000	After-cataract with vision obscured following extraction of cataract	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
37108933	15700000000000000	Bilateral after-cataract not obscuring vision	-	Yes	-
37169187	15700000000000000	Bilateral congenital capsular cataracts	-	Yes	-
37168350	1280000000	Congenital cataract microcornea with corneal opacity	-	Yes	-
37166820	1260000000	Congenital cataract, severe neonatal hepatopathy, global developmental delay syndrome	-	Yes	-
1246397	349000000000000	Congenital zonular cataract of left eye	-	Yes	-
1246393	348000000000000	Congenital zonular cataract of right eye	-	Yes	-
37169189	15700000000000000	Left congenital capsular cataract	-	Yes	-
37171332	341000000000000	Left congenital combined form cataract	-	Yes	-
37160969	1170000000	Microcephaly, congenital cataract, psoriasiform dermatitis syndrome	-	Yes	-
37169188	15700000000000000	Right congenital capsular cataract	-	Yes	-
37171272	336000000000000	Right congenital combined form cataract	-	Yes	-
37163794	1220000000	Cataract, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, skeletal dysplasia syndrome	-	Yes	-
1449315	1350000000	Intellectual disability, early-onset cataract, microcephaly syndrome	-	Yes	-
4194065	79385002	Lowe syndrome	-	Yes	-
37165629	1260000000	Oculocerebrodental syndrome	-	Yes	-
37163797	1220000000	Retinitis pigmentosa, juvenile cataract, short stature, intellectual disability syndrome	-	Yes	-

Depression

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
440383	35489007	Depressive disorder	Yes	-	Yes
4197222	79842004	Stuporous depression	-	Yes	-
4336980	87842000	Generalized neuromuscular exhaustion syndrome	-	Yes	-
4154805	322000000	Involutional depression	-	Yes	-
4057218	19694002	Late onset dysthymia	-	Yes	-
4338029	232000000	Masked depression	-	Yes	-
4133073	279000000	Maternity blues	-	Yes	-
4223090	84788008	Menopausal depression	-	Yes	-
4149320	310000000	Mild depression	-	Yes	-
4129842	237000000	Mild postnatal depression	-	Yes	-
36713698	719000000	Minimal depression	-	Yes	-
4224940	84760002	Schizoaffective disorder, depressive type	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
4092239	248000000	Seasonal affective disorder	-	Yes	-
4224639	85080004	Secondary dysthymia	-	Yes	-
4150047	3109008	Secondary dysthymia early onset	-	Yes	-
4263770	36170009	Secondary dysthymia late onset	-	Yes	-
4149321	310000000	Severe depression	-	Yes	-
4129184	237000000	Severe postnatal depression	-	Yes	-
44782720	133000000000000	Severe seasonal affective disorder	-	Yes	-
607540	1150000000	Treatment resistant depression	-	Yes	-
439251	192000000	Bipolar affective disorder, currently depressed, in full remission	-	Yes	-
44782943	699000000	Depressive disorder in remission	-	Yes	-
4269493	63412003	Major depression in full remission	-	Yes	-
4148630	30605009	Major depression in partial remission	-	Yes	-
4176002	42810003	Major depression in remission	-	Yes	-
4323418	70747007	Major depression single episode, in partial remission	-	Yes	-
42534817	105000000000000	Postpartum major depression in remission	-	Yes	-
4145216	427000000	Premenstrual dysphoric disorder in remission	-	Yes	-
4263748	46244001	Recurrent major depression in full remission	-	Yes	-
4141454	33135002	Recurrent major depression in partial remission	-	Yes	-
433991	68019004	Recurrent major depression in remission	-	Yes	-
35615154	163000000000000000	Recurrent major depressive disorder co-occurrent with anxiety in full remission	-	Yes	-
35615155	163000000000000000	Recurrent major depressive disorder in partial remission co-occurrent with anxiety	-	Yes	-
44805549	765000000000000	Recurrent major depressive episodes, in partial remission	-	Yes	-
44813499	765000000000000	Recurrent major depressive episodes, in remission	-	Yes	-
44805669	755000000000000	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission	-	Yes	-
4025677	19527009	Single episode of major depression in full remission	-	Yes	-
44805550	765000000000000	Single major depressive episode, in remission	-	Yes	-
44805668	755000000000000	Single major depressive episode, severe, with psychosis, psychosis in remission	-	Yes	-
37109950	724000000	Mood disorder with depressive symptoms caused by alcohol	-	Yes	-
3654788	839000000	Mood disorder with depressive symptoms caused by amphetamine and/or amphetamine derivative	-	Yes	-
37110429	725000000	Mood disorder with depressive symptoms caused by anxiolytic	-	Yes	-
37110438	725000000	Mood disorder with depressive symptoms caused by cocaine	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
42538604	762000000	Mood disorder with depressive symptoms caused by dissociative drug	-	Yes	-
42538596	762000000	Mood disorder with depressive symptoms caused by hallucinogen	-	Yes	-
37110428	725000000	Mood disorder with depressive symptoms caused by hypnotic	-	Yes	-
42538584	762000000	Mood disorder with depressive symptoms caused by opioid	-	Yes	-
37117211	725000000	Mood disorder with depressive symptoms caused by sedative	-	Yes	-
42538590	762000000	Mood disorder with depressive symptoms caused by stimulant	-	Yes	-
42538736	763000000	Mood disorder with depressive symptoms caused by synthetic cathinone	-	Yes	-
42538599	762000000	Mood disorder with depressive symptoms caused by volatile inhalant	-	Yes	-
37109952	724000000	Mood disorder with mixed manic and depressive symptoms caused by alcohol	-	Yes	-
37016718	713000000	Acute depression	-	Yes	-
4308866	83458005	Agitated depression	-	Yes	-
37312479	788000000	Antenatal depression	-	Yes	-
438727	192000000	Atypical depressive disorder	-	Yes	-
439254	192000000	Bipolar affective disorder, current episode depression	-	Yes	-
439253	192000000	Bipolar affective disorder, currently depressed, mild	-	Yes	-
437528	192000000	Bipolar affective disorder, currently depressed, moderate	-	Yes	-
4107538	29929003	Bipolar I disorder, most recent episode depressed with atypical features	-	Yes	-
4103574	192000000	Chronic depression	-	Yes	-
40481798	442000000	Chronic depressive personality disorder	-	Yes	-
4131545	413000000	Depression requiring intervention	-	Yes	-
4333687	232000000	Depressive conduct disorder	-	Yes	-
440383	35489007	Depressive disorder	-	Yes	-
37209503	162000000000000000	Depressive disorder caused by amphetamine	-	Yes	-
4103126	191000000	Depressive disorder caused by drug	-	Yes	-
45757213	108000000000000000	Depressive disorder in mother complicating childbirth	-	Yes	-
37018656	94600000000000	Depressive disorder in mother complicating pregnancy	-	Yes	-
433440	78667006	Dysthymia	-	Yes	-
4096229	2506003	Early onset dysthymia	-	Yes	-
4114950	301000000	Endogenous depression	-	Yes	-
4168858	275000000	Endogenous depression - recurrent	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
4333679	231000000	Endogenous depression first episode	-	Yes	-
1340305	OMOP5165960	Exacerbation of depressive disorder	-	Yes	-
36712668	10200000000000	Perinatal depression	-	Yes	-
607543	1150000000	Persistent depressive disorder	-	Yes	-
4332994	231000000	Post-schizophrenic depression	-	Yes	-
37166876	1260000000	Postmenopausal depression	-	Yes	-
4305966	82218004	Postoperative depression	-	Yes	-
4239471	58703003	Postpartum depression	-	Yes	-
4102973	192000000	Postviral depression	-	Yes	-
4242733	596004	Premenstrual dysphoric disorder	-	Yes	-
4307951	83176005	Primary dysthymia	-	Yes	-
4243308	38451003	Primary dysthymia early onset	-	Yes	-
4195680	67711008	Primary dysthymia late onset	-	Yes	-
35622934	765000000	Psychosis and severe depression co-occurrent and due to bipolar affective disorder	-	Yes	-
4314692	87414006	Reactive depression (situational)	-	Yes	-
35609845	1090000000000000	Reactive depression, first episode	-	Yes	-
35609842	1090000000000000	Reactive depression, prolonged single episode	-	Yes	-
35609844	1090000000000000	Reactive depression, recurrent	-	Yes	-
35609843	1090000000000000	Reactive depression, single episode	-	Yes	-
435520	192000000	Reactive depressive psychosis	-	Yes	-
43020483	289000000000000	Reactive depressive psychosis, single episode	-	Yes	-
4226155	40568001	Recurrent brief depressive disorder	-	Yes	-
4098302	192000000	Recurrent depression	-	Yes	-
35610109	1090000000000000	Recurrent depression with current moderate episode	-	Yes	-
35610097	1090000000000000	Recurrent depression with current severe episode and psychotic features	-	Yes	-
35610108	1090000000000000	Recurrent depression with current severe episode without psychotic features	-	Yes	-
37309680	16200000000000000	Depressive disorder caused by methamphetamine	-	Yes	-
4174987	48589009	Minor depressive disorder	-	Yes	-
4338031	232000000	Mixed anxiety and depressive disorder	-	Yes	-
4151170	310000000	Moderate depression	-	Yes	-
37164792	1230000000	Mood disorder with depressive symptoms caused by ethanol	-	Yes	-
443864	14070001	Multi-infarct dementia with depression	-	Yes	-
45757195	10800000000000000	Major depressive disorder in mother complicating childbirth	-	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude	Prevalent
45757196	10800000000000000	Major depressive disorder in mother complicating pregnancy	-	Yes	-
36717092	720000000	Moderately severe depression	-	Yes	-
35609824	1090000000000000	Recurrent reactive depressive episodes, severe, with psychosis	-	Yes	-

Anxiety

Concept ID	Concept Code	Concept Name	Descendants	Exclude	Prevalent
442077	197000000	Anxiety disorder	Yes	-	Yes
4245974	59923000	Panic disorder with agoraphobia AND panic attacks in full remission	-	Yes	-
4002897	11941006	Panic disorder with agoraphobia, agoraphobic avoidance in full remission AND panic attacks in full remission	-	Yes	-
4085666	24781009	Panic disorder with agoraphobia, mild agoraphobic avoidance AND panic attacks in full remission	-	Yes	-
4272328	64060000	Panic disorder with agoraphobia, moderate agoraphobic avoidance AND panic attacks in full remission	-	Yes	-
4243153	38328002	Panic disorder with agoraphobia, severe agoraphobic avoidance AND panic attacks in full remission	-	Yes	-
4221253	82494000	Panic disorder without agoraphobia with panic attacks in full remission	-	Yes	-
35615154	16300000000000000	Recurrent major depressive disorder co-occurrent with anxiety in full remission	-	Yes	-
37110440	725000000	Obsessive compulsive disorder caused by cocaine	-	Yes	-
37110473	725000000	Obsessive compulsive disorder caused by psychoactive substance	-	Yes	-
42538593	762000000	Obsessive compulsive disorder caused by stimulant	-	Yes	-
42538739	763000000	Obsessive compulsive disorder caused by synthetic cathinone	-	Yes	-
40486521	446000000	Acute posttraumatic stress disorder following military combat	-	Yes	-
44783184	699000000	Chronic post-traumatic stress disorder following military combat	-	Yes	-
40486886	446000000	Delayed posttraumatic stress disorder following military combat	-	Yes	-
4247433	61157009	Combat fatigue	-	Yes	-
4219044	82339009	Amphetamine-induced anxiety disorder	-	Yes	-
4146660	34938008	Anxiety disorder caused by alcohol	-	Yes	-

Concept ID	Concept Code	Concept Name	Descendants	Exclude	Prevalent
4198826	51493001	Anxiety disorder caused by cocaine	-	Yes	-
37110465	725000000	Anxiety disorder caused by dissociative drug	-	Yes	-
37110466	725000000	Anxiety disorder caused by ketamine	-	Yes	-
4135202	3158007	Panic disorder with agoraphobia, agoraphobic avoidance in partial remission AND panic attacks in partial remission	-	Yes	-
37309777	12400000000000000	Anxiety disorder caused by methamphetamine	-	Yes	-
37110453	725000000	Anxiety disorder caused by methylenedioxymethamphetamine	-	Yes	-
37119146	725000000	Anxiety disorder caused by opioid	-	Yes	-
4206779	55967005	Anxiety disorder caused by phencyclidine	-	Yes	-
42538592	762000000	Anxiety disorder caused by stimulant	-	Yes	-
42537777	737000000	Anxiety disorder caused by synthetic cannabinoid	-	Yes	-
42538738	763000000	Anxiety disorder caused by synthetic cathinone	-	Yes	-
3171318	9970000000000000	Anxiety disorder due to brain injury	-	Yes	-
601870	472000000000000	Anxiety disorder due to severe acute respiratory syndrome coronavirus 2	-	Yes	-
45757095	10700000000000000	Anxiety disorder in mother complicating childbirth	-	Yes	-
4323299	70655008	Caffeine-induced anxiety disorder	-	Yes	-
4221077	39951001	Cannabis-induced anxiety disorder	-	Yes	-
4035299	15277004	Hallucinogen-induced anxiety disorder	-	Yes	-
4049341	20876004	Inhalant-induced anxiety disorder	-	Yes	-
4178114	50026000	Organic anxiety disorder caused by psychoactive substance	-	Yes	-
4102965	192000000	Acute fugue state due to acute stress reaction	-	Yes	-
4099956	192000000	Acute panic state due to acute stress reaction	-	Yes	-
4102966	192000000	Acute stupor state due to acute stress reaction	-	Yes	-
4008568	111000000	Panic disorder with agoraphobia, agoraphobic avoidance in full remission AND panic attacks in partial remission	-	Yes	-
4329036	22230001	Panic disorder with agoraphobia, agoraphobic avoidance in partial remission AND panic attacks in full remission	-	Yes	-

Pulmonary exacerbation

Concept id	Concept Code	Concept Name	Descendants	Exclude
Pulmonary exacerbation				
3183290	13840001000004105	Pulmonary exacerbation cystic fibrosis	Yes	-
CF lung disease				
254320	86555001	Cystic fibrosis of the lung	Yes	-
Respiratory infection				
45768834	707351006	Institution-acquired respiratory infection	Yes	-
4133224	278516003	Lobar pneumonia	Yes	-
25297	363746003	Acute pharyngitis	Yes	-
4112341	195647007	Acute respiratory infections	Yes	-
4181583	54150009	Upper respiratory infection	Yes	-
4193169	312133006	Viral respiratory infection	Yes	-
4193174	312149008	Fungal respiratory infection	Yes	-
4207184	312117008	Bacterial respiratory infection	Yes	-
35624318	766983005	Susceptibility to respiratory infection associated with CD8alpha chain mutation	Yes	Yes
44788779	201031000000000	Asthma trigger - respiratory infection	Yes	Yes
37017244	713484001	Disorder of respiratory system co-occurrent with human immunodeficiency virus infection	Yes	Yes
42598979	344131000000000	Enzootic pneumonia of calves	-	Yes
42599237	349401000000000	Feline infectious peritonitis AND pleuritis	-	Yes
42599228	349061000000000	Feline pneumonitis	-	Yes
42572450	336491000000000	Feline viral rhinotracheitis	-	Yes
42598956	343771000000000	Inclusion body rhinitis of swine	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
42600374	45381000000000	Infection of gill with Chlamydiales-like bacteria	-	Yes
42574269	45641000000000	Infection of respiratory tract by Aspergillus	-	Yes
42598864	341511000000000	Infectious avian bronchitis	-	Yes
42599268	350011000000000	Infectious avian laryngotracheitis	-	Yes
42599106	346381000000000	Infectious bovine rhinotracheitis	-	Yes
42599561	357061000000000	Tuberculous pneumonia of animals	-	Yes
40481431	443378001	Lady Windermere syndrome	-	Yes
42600088	41281000000000	Bacterial pyothorax	-	Yes
42598991	344291000000000	Brooder pneumonia	-	Yes
42599092	34621000000000	Choanal mass due to Trichomonas infection	-	Yes
42598854	341001000000000	Chronic respiratory disease due to Mycoplasma gallisepticum	-	Yes
42599657	358011000000000	Influenza caused by Canine Influenza A virus	-	Yes
42572672	337301000000000	Murine chronic respiratory disease	-	Yes
42573218	359921000000000	Mycoplasmal pneumonia	-	Yes
42573178	355231000000000	Pneumonia due to Mannheimia haemolytica	-	Yes
4115044	285381006	Acute infective exacerbation of chronic obstructive pulmonary disease	-	Yes
37116455	733170007	Chronic aspergillosis of paranasal sinus	-	Yes
37160741	1163150009	Chronic cavitary pulmonary aspergillosis	-	Yes
45757644	28791000000000	Chronic coccidioidomycotic pneumonia	-	Yes
37160739	1163147006	Chronic fibrosing pulmonary aspergillosis	-	Yes
4049243	232434002	Chronic fungal laryngitis	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
4110027	195770009	Chronic infective rhinitis	-	Yes
4048188	232406009	Chronic pharyngeal candidiasis	-	Yes
4221767	417688002	Chronic progressive coccidioidal pneumonia	-	Yes
4084973	240742009	Chronic pulmonary African histoplasmosis	-	Yes
37118654	733171006	Chronic pulmonary aspergillosis	-	Yes
4080753	240747003	Chronic pulmonary blastomycosis	-	Yes
260034	233615002	Chronic pulmonary coccidioidomycosis	-	Yes
4096917	26427008	Chronic pulmonary histoplasmosis	-	Yes
4110056	196001008	Chronic obstructive pulmonary disease with acute lower respiratory infection	-	Yes
4174309	276693005	Congenital bacterial pneumonia	-	Yes
4070540	206289001	Congenital chlamydial pneumonia	-	Yes
4048148	206286008	Congenital Escherichia coli pneumonia	-	Yes
4048147	206284006	Congenital group A hemolytic streptococcal pneumonia	-	Yes
4071611	206285007	Congenital group B hemolytic streptococcal pneumonia	-	Yes
4048149	206287004	Congenital pseudomonal pneumonia	-	Yes
4188480	47082005	Congenital rubella pneumonia	-	Yes
4071610	206283000	Congenital staphylococcal pneumonia	-	Yes
4167920	275376007	Congenital syphilitic chronic coryza	-	Yes
4080886	276700005	Congenital syphilitic rhinitis	-	Yes
4174308	276692000	Congenital viral pneumonia	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
320752	61700007	Influenza with non-respiratory manifestation	-	Yes
42573020	349781000000000	Porcine contagious pleuropneumonia	-	Yes
42572644	336161000000000	Pulmonary abscess due to Rhodococcus	-	Yes
42575809	335271000000000	Pulmonary adenomatosis of sheep	-	Yes
42598908	342641000000000	Chronic viral encephalomyelitis of sheep	-	Yes
42572881	344871000000000	Contagious bovine pleuropneumonia	-	Yes
42599199	348481000000000	Contagious caprine pleuropneumonia	-	Yes
42599060	345621000000000	Enzootic mycoplasmal pneumonia of swine	-	Yes
Respiratory diagnosis				
312437	267000000	Dyspnea	Yes	-
4059017	162000000	Productive cough-yellow sputum	Yes	-
4060051	162000000	Productive cough -green sputum	Yes	-
4077373	276000000	Sputum evidence of infection	Yes	-
4080153	278000000	Thick sputum	Yes	-
4172486	42192008	Purulent sputum	Yes	-
4174289	278000000	Green sputum	Yes	-
45768834	707000000	Institution-acquired respiratory infection	Yes	-
4133224	279000000	Lobar pneumonia	Yes	-
25297	364000000	Acute pharyngitis	Yes	-
4112341	196000000	Acute respiratory infections	Yes	-
4181583	54150009	Upper respiratory infection	Yes	-
4193169	312000000	Viral respiratory infection	Yes	-
4193174	312000000	Fungal respiratory infection	Yes	-
4207184	312000000	Bacterial respiratory infection	Yes	-
433596	275000000	Abnormal sputum	Yes	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
4116781	301000000	Difficulty in coughing up sputum	Yes	Yes
4222908	401000000	Borg Breathlessness Score: 0 none at all	Yes	Yes
4221237	401000000	Borg Breathlessness Score: 0.5 very, very slight (just noticeable)	Yes	Yes
4222444	401000000	Borg Breathlessness Score: 1 very slight	Yes	Yes
4228754	422000000	Dyspnea with AIDS (acquired immunodeficiency syndrome)	Yes	Yes
44809070	852000000000000	Minimal breathlessness	Yes	Yes
36685567	1100000000000000	mMRC (modified Medical Research Council) dyspnoea scale grade 0	Yes	Yes
315361	62744007	Orthopnea	Yes	Yes
4148800	30744009	Platypnea	Yes	Yes
4010972	103000000	Trepopnea	Yes	Yes
35624318	767000000	Susceptibility to respiratory infection associated with CD8alpha chain mutation	Yes	Yes
44788779	201000000000000	Asthma trigger - respiratory infection	Yes	Yes
37017244	713000000	Disorder of respiratory system co-occurrent with human immunodeficiency virus infection	Yes	Yes
4110056	196000000	Chronic obstructive pulmonary disease with acute lower respiratory infection	-	Yes
4174309	277000000	Congenital bacterial pneumonia	-	Yes
4070540	206000000	Congenital chlamydial pneumonia	-	Yes
4048148	206000000	Congenital Escherichia coli pneumonia	-	Yes
4048147	206000000	Congenital group A hemolytic streptococcal pneumonia	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
4071611	206000000	Congenital group B hemolytic streptococcal pneumonia	-	Yes
4048149	206000000	Congenital pseudomonal pneumonia	-	Yes
4188480	47082005	Congenital rubella pneumonia	-	Yes
4071610	206000000	Congenital staphylococcal pneumonia	-	Yes
4167920	275000000	Congenital syphilitic chronic coryza	-	Yes
4080886	277000000	Congenital syphilitic rhinitis	-	Yes
4174308	277000000	Congenital viral pneumonia	-	Yes
320752	61700007	Influenza with non-respiratory manifestation	-	Yes
42573020	350000000000000	Porcine contagious pleuropneumonia	-	Yes
42572644	336000000000000	Pulmonary abscess due to Rhodococcus	-	Yes
42575809	335000000000000	Pulmonary adenomatosis of sheep	-	Yes
42598908	343000000000000	Chronic viral encephalomyelitis of sheep	-	Yes
42572881	345000000000000	Contagious bovine pleuropneumonia	-	Yes
42599199	348000000000000	Contagious caprine pleuropneumonia	-	Yes
42599060	346000000000000	Enzootic mycoplasmal pneumonia of swine	-	Yes
42598979	344000000000000	Enzootic pneumonia of calves	-	Yes
42599237	349000000000000	Feline infectious peritonitis AND pleuritis	-	Yes
42599228	349000000000000	Feline pneumonitis	-	Yes
42572450	336000000000000	Feline viral rhinotracheitis	-	Yes
42598956	344000000000000	Inclusion body rhinitis of swine	-	Yes
42600374	45400000000000	Infection of gill with Chlamydiales-like bacteria	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
42574269	45600000000000	Infection of respiratory tract by Aspergillus	-	Yes
42598864	342000000000000	Infectious avian bronchitis	-	Yes
42599268	350000000000000	Infectious avian laryngotracheitis	-	Yes
42599106	346000000000000	Infectious bovine rhinotracheitis	-	Yes
42599561	357000000000000	Tuberculous pneumonia of animals	-	Yes
40481431	443000000	Lady Windermere syndrome	-	Yes
42600088	41300000000000	Bacterial pyothorax	-	Yes
42598991	344000000000000	Brooder pneumonia	-	Yes
42599092	34600000000000	Choanal mass due to Trichomonas infection	-	Yes
42598854	341000000000000	Chronic respiratory disease due to Mycoplasma gallisepticum	-	Yes
42599657	358000000000000	Influenza caused by Canine Influenza A virus	-	Yes
42572672	337000000000000	Murine chronic respiratory disease	-	Yes
42573218	360000000000000	Mycoplasmal pneumonia	-	Yes
42573178	355000000000000	Pneumonia due to Mannheimia haemolytica	-	Yes
4115044	285000000	Acute infective exacerbation of chronic obstructive pulmonary disease	-	Yes
37116455	733000000	Chronic aspergillosis of paranasal sinus	-	Yes
37160741	1160000000	Chronic cavitary pulmonary aspergillosis	-	Yes
45757644	28800000000000	Chronic coccidioidomycotic pneumonia	-	Yes
37160739	1160000000	Chronic fibrosing pulmonary aspergillosis	-	Yes
4049243	232000000	Chronic fungal laryngitis	-	Yes
4110027	196000000	Chronic infective rhinitis	-	Yes
4048188	232000000	Chronic pharyngeal candidiasis	-	Yes

Concept id	Concept Code	Concept Name	Descendants	Exclude
4221767	418000000	Chronic progressive coccidioidal pneumonia	-	Yes
4084973	241000000	Chronic pulmonary African histoplasmosis	-	Yes
37118654	733000000	Chronic pulmonary aspergillosis	-	Yes
4080753	241000000	Chronic pulmonary blastomycosis	-	Yes
260034	234000000	Chronic pulmonary coccidioidomycosis	-	Yes
4096917	26427008	Chronic pulmonary histoplasmosis	-	Yes
Type of visit				
9202	OP	Outpatient Visit	Yes	-
9203	ER	Emergency Room Visit	Yes	-
*Antibiotics (listed by ingredient)**				
46221507	1603834	avibactam	Yes	-
46274210	1040004	ceftaroline fosamil	Yes	-
45892599	1597609	ceftolozane	Yes	-
45892419	1596450	gentamicin	Yes	1592219, 1592226, 42620715, 41236476, 43135095, 1466221, 1594689, 41267385, 42970795, 36266913, 21142636, 44054609, 21122844, 40745776, 21034617, 41080142, 40745786, 1594501, 1594375, 1594393, 41142987, 41080141, 1594402, 44094575, 41173995, 40718641, 40830690, 40861880, 40860698, 41079116, 41110492, 41110491, 41266319, 41080248, 40986491, 41143083, 40924017, 41080164, 2059681, 41298399, 41080161, 41174008, 41111752, 41017766, 1594426, 40893250, 41049034, 35134453, 1594363, 40862000, 41111768, 41267731, 40830870, 36248836, 42963093, 42963090, 36248933, 40861896
1790868	641	amikacin	Yes	37499296, 36118706, 40721707, 2047724, 35858631, 35858630
1713332	723	amoxicillin	Yes	-
1734104	18631	azithromycin	Yes	35861664, 36212960, 40139853, 40144501, 43858131
1715117	1272	aztreonam	Yes	41118896, 41317706, 40869145, 41286376, 43173476, 42483137, 36212965
1771162	2180	cefazolin	Yes	1235640
1796458	25037	cefdinir	Yes	-
1748975	20481	cefepime	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
1775741	2189	cefoxitin	Yes	-
1776684	2191	ceftazidime	Yes	21132307
1778162	2194	cefuroxime	Yes	36217283
1786621	2231	cephalexin	Yes	-
1797513	2551	ciprofloxacin	Yes	36217286, 42479725, 36249233, 42965658, 36217287, 43258666, 36269500, 36217289, 36217292, 43605428, 35857840, 35857832, 35857838, 35857844
1759842	48203	clavulanate	Yes	-
997881	2582	clindamycin	Yes	36409570, 21140538, 1234254, 36216357, 21111150, 42613529, 2934751, 1234263, 2934750, 35873678, 36216359, 41143146, 35873672, 35873683, 42479727, 36216363, 44055989, 36216364, 43603372, 1970313, 44187011, 41111768, 41267731, 746967, 44043303, 36217621, 40830871, 21160318
901845	2709	colistin	Yes	41111587, 42948109, 41267536, 36214841, 35142897, 35158846, 36812255, 36058981, 36811551, 2906262, 21145117, 21105903, 36888521, 43030062, 21155060, 40737589, 43030076, 1234423, 43177386, 35129793, 43215034, 36269497
1724666	3356	dicloxacillin	Yes	-
1713905	119771	doripenem	Yes	-
1738521	3640	doxycycline	Yes	40150291, 35861018, 41017904, 36933616
1717963	325642	ertapenem	Yes	-
1778262	5690	imipenem	Yes	-
1742253	82122	levofloxacin	Yes	36962141, 44120448, 35861002, 36221026, 35860990, 43678432, 44135460, 36922933, 36958160, 1971418
1736887	190376	linezolid	Yes	-
1709170	29561	meropenem	Yes	-
1708880	6980	minocycline	Yes	40065421, 35156943, 2052922, 37497504, 2052920
1716903	139462	moxifloxacin	Yes	36213853, 43606620
1713930	7233	nafcillin	Yes	-
1724703	7773	oxacillin	Yes	-
1746114	8339	piperacillin	Yes	-
1836430	10180	sulfamethoxazole	Yes	36227260, 35858133, 35858117, 35858134
1741122	37617	tazobactam	Yes	-

Concept id	Concept Code	Concept Name	Descendants	Exclude
1836948	10395	tetracycline	Yes	1234269, 41048539, 1234412, 36221750, 1235660, 36221752, 35857993, 35131575, 40830335, 35158972, 36221757, 41236438, 41173962, 1234807, 35830590, 40862308, 41497802, 41500127, 41496213, 41500555, 41496602, 41498942, 41049155, 40838347, 40850155, 40962881, 42728898, 41017627, 35151073
1742432	384455	tigecycline	Yes	-
902722	10627	tobramycin	Yes	40958505, 41183147, 44169216, 44053751, 42480133, 36214118, 44042662, 36214120, 35770401, 43674454, 40754915, 36214121, 1831782, 36222594, 36215046, 42481931, 44197593, 36224794
1705674	10829	trimethoprim	Yes	35862748, 36225305
792531	1945213	vaborbactam	Yes	-
1707687	11124	vancomycin	Yes	35144660, 21140439, 40752961

*Only systemic antibiotics were included. Non-systemic products and their descendants were excluded from the concept sets.

ANNEX II: Supplementary Tables

Table S1. Characteristics of individuals at the date of the first recorded prescription of any CFTR modulator following CF, stratified by paediatric and adult populations, per data source, 2015–2024.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Paediatric population (<18 years)							
Number of subjects	43	57	14	23	97	11	<5
Age (years), median [q25–q75]	11 [5–14]	12 [8–13]	11 [7–12]	12 [10–13]	11 [7–14]	14 [12–16]	0 [0–0]
Age (years), range (min–max)	1 to 17	2 to 17	2 to 17	2 to 17	1 to 17	3 to 17	0 to 0
Sex, n (%)							
• Females	23 (53.49%)	29 (50.88%)	5 (35.71%)	10 (43.48%)	49 (50.52%)	7 (63.64%)	<5
• Males	20 (46.51%)	28 (49.12%)	9 (64.29%)	13 (56.52%)	48 (49.48%)	<5	-
Adult population (≥ 18 years)							
Number of subjects	39	39	157	84	176	48	12
Age (years), median [q25–q75]	32 [26–36]	26 [21–30]	35 [28–41]	31 [25–41]	34 [26–44]	31 [26–39]	36 [30–45]
Age (years), range (min–max)	18 to 67	18 to 48	18 to 62	18 to 55	18 to 82	18 to 72	22 to 60
Sex, n (%)							
• Females	18 (46.15%)	25 (64.10%)	94 (59.87%)	46 (54.76%)	77 (43.75%)	31 (64.58%)	6 (50.00%)
• Males	21 (53.85%)	14 (35.90%)	63 (40.13%)	38 (45.24%)	99 (56.25%)	17 (35.42%)	6 (50.00%)

APHM = Assistance Publique–Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

Table S2. Characteristics of individuals at the date of the first recorded ivacaftor prescription following CF diagnosis, stratified by paediatric and adult populations, per data source, 2015–2024.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Paediatric population (<18 years)							
Number of subjects	15	6	7	12	65	10	<5
Age (years), median [q25–q75]	10 [8–12]	13 [11–16]	11 [10–12]	10 [8–13]	12 [8–14]	14 [12–16]	0 [0–0]
Age (years), range (min–max)	4 to 17	9 to 17	8 to 17	2 to 17	6 to 17	3 to 17	0 to 0
Sex, n (%)							
• Females	10 (66.67%)	<5	<5	8 (66.67%)	32 (49.23%)	6 (60.00%)	<5
• Males	5 (33.33%)	<5	<5	<5	33 (50.77%)	<5	-
Adult population (≥ 18 years)							
Number of subjects	14	12	115	51	143	45	10
Age (years), median [q25–q75]	35 [33–42]	25 [22–27]	35 [28–42]	35 [29–44]	36 [28–45]	31 [27–40]	34 [29 - 40]
Age (years), range (min–max)	18 to 67	18 to 38	18 to 62	18 to 55	18 to 82	18 to 72	22 to 60
Sex, n (%)							
• Females	5 (35.71%)	7 (58.33%)	65 (56.52%)	30 (58.82%)	61 (42.66%)	30 (66.67%)	5 (50.00%)
• Males	9 (64.29%)	5 (41.67%)	50 (43.48%)	21 (41.18%)	82 (57.34%)	15 (33.33%)	5 (50.00%)

APHM = Assistance Publique–Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

Table S3. Characteristics of individuals at the date of the first recorded ivacaftor and lumacaftor prescription following CF diagnosis, stratified by paediatric and adult populations, per data source, 2015–2024.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Paediatric population (<18 years)							
Number of subjects	28	34	6	11	25	-	-
Age (years), median [q25–q75]	12 [4–14]	11 [6–12]	6 [3–10]	12 [12–14]	12 [5–16]	-	-
Age (years), range (min–max)	1 to 17	2 to 17	2 to 15	11 to 16	1 to 17	-	-
Sex, n (%)							
• Females	13 (46.43%)	19 (55.88%)	<5	<5	12 (48.00%)	-	-
• Males	15 (53.57%)	15 (44.12%)	<5	9 (81.82%)	13 (52.00%)	-	-
Adult population (≥ 18 years)							
Number of subjects	20	19	35	29	22	-	<5
Age (years), median [q25–q75]	28 [23–32]	24 [21–29]	32 [27–39]	27 [24–32]	23 [22–40]	-	0 [0–0]
Age (years), range (min–max)	18 to 59	18 to 48	19 to 49	18 to 45	18 to 44	-	0 to 0
Sex, n (%)							
• Females	10 (50.00%)	13 (68.42%)	23 (65.71%)	15 (51.72%)	7 (31.82%)	-	-
• Males	10 (50.00%)	6 (31.58%)	12 (34.29%)	14 (48.28%)	15 (68.18%)	-	<5

APHM = Assistance Publique–Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

Table S4. Characteristics of individuals at the date of the first recorded ivacaftor and tezacaftor prescription following CF diagnosis, stratified by paediatric and adult populations, per data source, 2015–2024.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Paediatric population (<18 years)							
Number of subjects	-	<5	-	-	-	-	-
Age (years), median [q25–q75]	-	0 [0 - 0]	-	-	-	-	-
Age (years), range (min–max)	-	0 to 0	-	-	-	-	-
Sex, n (%)							
• Females	-	<5	-	-	-	-	-
• Males	-	<5	-	-	-	-	-
Adult population (≥ 18 years)							
Number of subjects	-	-	37	-	<5	-	6
Age (years), median [q25–q75]	-	-	37 [28 - 43]	-	0 [0 - 0]	-	30 [25 - 36]
Age (years), range (min–max)	-	-	20 to 62	-	0 to 0	-	22 to 56
Sex, n (%)							
• Females	-	-	23 (62.16%)	-	<5	-	<5
• Males	-	-	14 (37.84%)	-	<5	-	<5

APHM = Assistance Publique–Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

Table S5. Characteristics of individuals at the date of the first recorded ivacaftor, tezacaftor and elexacaftor prescription following CF diagnosis, stratified by paediatric and adult populations, per data source, 2015–2024.

Variable	APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Paediatric population (<18 years)							
Number of subjects	13	19	6	<5	67	7	-
Age (years), median [q25–q75]	10 [7–12]	12 [10–14]	11 [9–13]	0 [0–0]	11 [8–14]	14 [13–16]	-
Age (years), range (min–max)	4 to 17	2 to 16	8 to 17	0 to 0	6 to 17	12 to 17	-
Sex, n (%)							
• Females	9 (69.23%)	8 (42.11%)	<5	<5	37 (55.22%)	<5	-
• Males	<5	11 (57.89%)	<5	-	30 (44.78%)	<5	-
Adult population (≥ 18 years)							
Number of subjects	18	9	78	18	131	30	-
Age (years), median [q25–q75]	34 [30–42]	32 [26–36]	34 [28–41]	32 [25–45]	35 [28–44]	31 [27–37]	-
Age (years), range (min–max)	18 to 67	19 to 47	19 to 62	18 to 55	18 to 82	18 to 72	-
Sex, n (%)							
• Females	8 (44.44%)	5 (55.56%)	44 (56.41%)	7 (38.89%)	56 (42.75%)	20 (66.67%)	-
• Males	10 (55.56%)	<5	34 (43.59%)	11 (61.11%)	75 (57.25%)	10 (33.33%)	-

APHM = Assistance Publique–Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

Table S6. Frequency of supportive CF therapies use in individuals on ivacaftor across different pre- and post-index windows, in the overall population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	20 (68.97%)	11 (37.93%)	10 (34.48%)	<5	<5	5 (17.24%)	6 (20.69%)
CDW Bordeaux	n (%)	10 (55.56%)	5 (27.78%)	<5	6 (33.33%)	6 (33.33%)	7 (38.89%)	7 (38.89%)
IQVIA DA Germany	n (%)	40 (32.79%)	27 (22.13%)	<5	<5	11 (9.02%)	20 (16.39%)	42 (34.43%)
POLIMI	n (%)	49 (77.78%)	42 (66.67%)	37 (58.73%)	37 (58.73%)	37 (58.73%)	39 (61.90%)	40 (63.49%)
NLHR	n (%)	85 (40.87%)	57 (27.40%)	<5	13 (6.25%)	36 (17.31%)	52 (25.00%)	59 (28.37%)
H12O	n (%)	37 (67.27%)	22 (40.00%)	8 (14.55%)	-	7 (12.73%)	14 (25.45%)	21 (38.18%)
CPRD GOLD	n (%)	6 (54.55%)	<5	0	<5	<5	<5	6 (54.55%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	<5
CDW Bordeaux	n (%)	15 (83.33%)	9 (50.00%)	6 (33.33%)	11 (61.11%)	12 (66.67%)	12 (66.67%)	13 (72.22%)
IQVIA DA Germany	n (%)	65 (53.28%)	40 (32.79%)	7 (5.74%)	10 (8.20%)	25 (20.49%)	34 (27.87%)	47 (38.52%)
POLIMI	n (%)	29 (46.03%)	22 (34.92%)	19 (30.16%)	17 (26.98%)	17 (26.98%)	17 (26.98%)	18 (28.57%)
NLHR	n (%)	161 (77.40%)	131 (62.98%)	12 (5.77%)	44 (21.15%)	79 (37.98%)	118 (56.73%)	124 (59.62%)
H12O	n (%)	25 (45.45%)	13 (23.64%)	9 (16.36%)	<5	<5	6 (10.91%)	9 (16.36%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	22 (75.86%)	14 (48.28%)	7 (24.14%)	<5	<5	7 (24.14%)	8 (27.59%)
CDW Bordeaux	n (%)	12 (66.67%)	5 (27.78%)	<5	6 (33.33%)	7 (38.89%)	7 (38.89%)	8 (44.44%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	63 (51.64%)	44 (36.07%)	<5	<5	16 (13.11%)	37 (30.33%)	56 (45.90%)
POLIMI	n (%)	33 (52.38%)	23 (36.51%)	16 (25.40%)	15 (23.81%)	15 (23.81%)	15 (23.81%)	19 (30.16%)
NLHR	n (%)	157 (75.48%)	121 (58.17%)	7 (3.37%)	25 (12.02%)	63 (30.29%)	108 (51.92%)	113 (54.33%)
H12O	n (%)	34 (61.82%)	23 (41.82%)	18 (32.73%)	8 (14.55%)	10 (18.18%)	15 (27.27%)	21 (38.18%)
CPRD GOLD	n (%)	9 (81.82%)	7 (63.64%)	0	<5	6 (54.55%)	9 (81.82%)	10 (90.91%)
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	14 (51.85%)	9 (33.33%)	6 (22.22%)	0	<5	<5	<5
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	56 (48.28%)	37 (31.90%)	<5	5 (4.31%)	22 (18.97%)	42 (36.21%)	57 (49.14%)
POLIMI	n (%)	24 (38.10%)	24 (38.10%)	24 (38.10%)	23 (36.51%)	23 (36.51%)	24 (38.10%)	24 (38.10%)
NLHR	n (%)	20 (9.71%)	15 (7.28%)	-	<5	9 (4.37%)	14 (6.80%)	14 (6.80%)
H12O	n (%)	20 (40.00%)	11 (22.00%)	<5	<5	5 (10.00%)	7 (14.00%)	8 (16.00%)
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	12 (41.38%)	<5	<5	<5	<5	5 (17.24%)	6 (20.69%)
CDW Bordeaux	n (%)	12 (66.67%)	5 (27.78%)	<5	<5	6 (33.33%)	7 (38.89%)	7 (38.89%)
IQVIA DA Germany	n (%)	58 (47.54%)	25 (20.49%)	<5	<5	12 (9.84%)	20 (16.39%)	31 (25.41%)
POLIMI	n (%)	34 (53.97%)	22 (34.92%)	16 (25.40%)	20 (31.75%)	21 (33.33%)	21 (33.33%)	21 (33.33%)
NLHR	n (%)	66 (31.73%)	33 (15.87%)	0	<5	11 (5.29%)	21 (10.10%)	21 (10.10%)
H12O	n (%)	40 (72.73%)	26 (47.27%)	16 (29.09%)	13 (23.64%)	18 (32.73%)	24 (43.64%)	25 (45.45%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	<5	0	0	0	0	0
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	46 (73.02%)	46 (73.02%)	36 (57.14%)	36 (57.14%)	38 (60.32%)	40 (63.49%)	41 (65.08%)
NLHR	n (%)	137 (66.50%)	126 (61.17%)	17 (8.25%)	51 (24.76%)	102 (49.51%)	123 (59.71%)	132 (64.08%)
H12O	n (%)	43 (86.00%)	26 (52.00%)	13 (26.00%)	<5	13 (26.00%)	22 (44.00%)	27 (54.00%)
CPRD GOLD	n (%)	10 (90.91%)	9 (81.82%)	<5	<5	9 (81.82%)	10 (90.91%)	10 (90.91%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S7. Frequency of supportive CF therapies use in individuals on ivacaftor across different pre- and post-index windows, in paediatric population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	10 (66.67%)	5 (33.33%)	<5	0	<5	<5	<5
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	0	0	0	0	0	0	<5
POLIMI	n (%)	7 (58.33%)	7 (58.33%)	5 (41.67%)	<5	<5	<5	<5
NLHR	n (%)	24 (36.92%)	12 (18.46%)	<5	5 (7.69%)	9 (13.85%)	12 (18.46%)	12 (18.46%)
H12O	n (%)	6 (60.00%)	5 (50.00%)	<5	0	<5	<5	<5

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	-	-	-	-	-	-
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	0
CDW Bordeaux	n (%)	6 (100.00%)	<5	<5	5 (83.33%)	5 (83.33%)	5 (83.33%)	5 (83.33%)
IQVIA DA Germany	n (%)	<5	<5	0	<5	<5	<5	<5
POLIMI	n (%)	8 (66.67%)	7 (58.33%)	7 (58.33%)	6 (50.00%)	6 (50.00%)	6 (50.00%)	7 (58.33%)
NLHR	n (%)	59 (90.77%)	55 (84.62%)	<5	20 (30.77%)	36 (55.38%)	47 (72.31%)	51 (78.46%)
H12O	n (%)	7 (70.00%)	6 (60.00%)	5 (50.00%)	<5	<5	<5	5 (50.00%)
CPRD GOLD	n (%)	-	-	-	-	-	-	-
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	12 (80.00%)	9 (60.00%)	5 (33.33%)	<5	<5	<5	<5
CDW Bordeaux	n (%)	5 (83.33%)	<5	0	<5	<5	<5	<5
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5
POLIMI	n (%)	12 (100.00%)	12 (100.00%)	10 (83.33%)	8 (66.67%)	8 (66.67%)	8 (66.67%)	8 (66.67%)
NLHR	n (%)	44 (67.69%)	28 (43.08%)	<5	<5	14 (21.54%)	24 (36.92%)	24 (36.92%)
H12O	n (%)	10 (100.00%)	8 (80.00%)	5 (50.00%)	6 (60.00%)	7 (70.00%)	7 (70.00%)	8 (80.00%)
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	5 (35.71%)	<5	<5	0	0	0	0
CDW Bordeaux	n (%)	0	0	0	0	0	0	0

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	<5	<5	0	<5	<5	<5	5 (71.43%)
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	10 (15.38%)	8 (12.31%)	-	<5	5 (7.69%)	7 (10.77%)	7 (10.77%)
H12O	n (%)	<5	<5	<5	0	<5	<5	<5
CPRD GOLD	n (%)	-	-	-	-	-	-	-
Tobramycin								
APHM	n (%)	8 (53.33%)	<5	<5	<5	<5	<5	<5
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	0	0	0	0	0	0	0
POLIMI	n (%)	5 (41.67%)	<5	<5	<5	<5	<5	<5
NLHR	n (%)	27 (41.54%)	8 (12.31%)	0	<5	<5	<5	<5
H12O	n (%)	8 (80.00%)	5 (50.00%)	5 (50.00%)	5 (50.00%)	5 (50.00%)	5 (50.00%)	5 (50.00%)
CPRD GOLD	n (%)	-	-	-	-	-	-	-
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	10 (83.33%)	10 (83.33%)	5 (41.67%)	<5	5 (41.67%)	5 (41.67%)	6 (50.00%)
NLHR	n (%)	53 (81.54%)	52 (80.00%)	7 (10.77%)	20 (30.77%)	47 (72.31%)	54 (83.08%)	55 (84.62%)
H12O	n (%)	8 (80.00%)	8 (80.00%)	8 (80.00%)	<5	<5	<5	6 (60.00%)
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S8. Frequency of supportive CF therapies use in individuals on ivacaftor across different pre- and post-index windows, in adult population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	10 (71.43%)	6 (42.86%)	6 (42.86%)	<5	<5	<5	<5
CDW Bordeaux	n (%)	7 (58.33%)	<5	<5	5 (41.67%)	5 (41.67%)	6 (50.00%)	6 (50.00%)
IQVIA DA Germany	n (%)	40 (34.78%)	27 (23.48%)	<5	<5	11 (9.57%)	20 (17.39%)	41 (35.65%)
POLIMI	n (%)	42 (82.35%)	35 (68.63%)	32 (62.75%)	33 (64.71%)	33 (64.71%)	35 (68.63%)	36 (70.59%)
NLHR	n (%)	61 (42.66%)	45 (31.47%)	<5	8 (5.59%)	27 (18.88%)	40 (27.97%)	47 (32.87%)
H12O	n (%)	31 (68.89%)	17 (37.78%)	<5	<5	6 (13.33%)	12 (26.67%)	17 (37.78%)
CPRD GOLD	n (%)	5 (50.00%)	<5	0	<5	<5	<5	6 (60.00%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	<5
CDW Bordeaux	n (%)	9 (75.00%)	5 (41.67%)	<5	6 (50.00%)	7 (58.33%)	7 (58.33%)	8 (66.67%)
IQVIA DA Germany	n (%)	63 (54.78%)	38 (33.04%)	7 (6.09%)	8 (6.96%)	23 (20.00%)	31 (26.96%)	44 (38.26%)
POLIMI	n (%)	21 (41.18%)	15 (29.41%)	12 (23.53%)	11 (21.57%)	11 (21.57%)	11 (21.57%)	11 (21.57%)
NLHR	n (%)	102 (71.33%)	76 (53.15%)	8 (5.59%)	24 (16.78%)	43 (30.07%)	71 (49.65%)	73 (51.05%)
H12O	n (%)	18 (40.00%)	7 (15.56%)	<5	0	0	<5	<5
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	10 (71.43%)	5 (35.71%)	<5	0	<5	<5	<5
CDW Bordeaux	n (%)	7 (58.33%)	<5	<5	5 (41.67%)	6 (50.00%)	6 (50.00%)	7 (58.33%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	60 (52.17%)	42 (36.52%)	<5	<5	16 (13.91%)	36 (31.30%)	55 (47.83%)
POLIMI	n (%)	21 (41.18%)	11 (21.57%)	6 (11.76%)	7 (13.73%)	7 (13.73%)	7 (13.73%)	11 (21.57%)
NLHR	n (%)	113 (79.02%)	93 (65.03%)	5 (3.50%)	21 (14.69%)	49 (34.27%)	84 (58.74%)	89 (62.24%)
H12O	n (%)	24 (53.33%)	15 (33.33%)	13 (28.89%)	<5	<5	8 (17.78%)	13 (28.89%)
CPRD GOLD	n (%)	8 (80.00%)	6 (60.00%)	0	<5	5 (50.00%)	8 (80.00%)	9 (90.00%)
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	9 (69.23%)	8 (61.54%)	5 (38.46%)	0	<5	<5	<5
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	53 (48.62%)	34 (31.19%)	<5	<5	19 (17.43%)	39 (35.78%)	52 (47.71%)
POLIMI	n (%)	21 (41.18%)	21 (41.18%)	21 (41.18%)	20 (39.22%)	20 (39.22%)	21 (41.18%)	21 (41.18%)
NLHR	n (%)	10 (7.09%)	7 (4.96%)	-	<5	<5	7 (4.96%)	7 (4.96%)
H12O	n (%)	17 (42.50%)	8 (20.00%)	<5	<5	<5	5 (12.50%)	6 (15.00%)
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	<5	<5	<5	<5	<5	<5	<5
CDW Bordeaux	n (%)	8 (66.67%)	<5	0	<5	<5	<5	<5
IQVIA DA Germany	n (%)	58 (50.43%)	25 (21.74%)	<5	<5	12 (10.43%)	20 (17.39%)	31 (26.96%)
POLIMI	n (%)	29 (56.86%)	19 (37.25%)	14 (27.45%)	18 (35.29%)	18 (35.29%)	18 (35.29%)	18 (35.29%)
NLHR	n (%)	39 (27.27%)	25 (17.48%)	0	<5	9 (6.29%)	18 (12.59%)	18 (12.59%)
H12O	n (%)	32 (71.11%)	21 (46.67%)	11 (24.44%)	8 (17.78%)	13 (28.89%)	19 (42.22%)	20 (44.44%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	<5	0	0	0	0	0
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	36 (70.59%)	36 (70.59%)	31 (60.78%)	32 (62.75%)	33 (64.71%)	35 (68.63%)	35 (68.63%)
NLHR	n (%)	84 (59.57%)	74 (52.48%)	10 (7.09%)	31 (21.99%)	55 (39.01%)	69 (48.94%)	77 (54.61%)
H12O	n (%)	35 (87.50%)	18 (45.00%)	5 (12.50%)	<5	10 (25.00%)	18 (45.00%)	21 (52.50%)
CPRD GOLD	n (%)	9 (90.00%)	8 (80.00%)	<5	<5	8 (80.00%)	9 (90.00%)	9 (90.00%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S9. Frequency of supportive CF therapies use in individuals on ivacaftor and lumacaftor across different pre- and post-index windows, in the overall population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	28 (58.33%)	23 (47.92%)	18 (37.50%)	5 (10.42%)	5 (10.42%)	14 (29.17%)	21 (43.75%)
CDW Bordeaux	n (%)	16 (30.19%)	10 (18.87%)	7 (13.21%)	7 (13.21%)	7 (13.21%)	12 (22.64%)	17 (32.08%)
IQVIA DA Germany	n (%)	11 (26.83%)	7 (17.07%)	<5	<5	5 (12.20%)	9 (21.95%)	19 (46.34%)
POLIMI	n (%)	20 (50.00%)	18 (45.00%)	16 (40.00%)	22 (55.00%)	22 (55.00%)	22 (55.00%)	23 (57.50%)
NLHR	n (%)	8 (17.02%)	6 (12.77%)	<5	<5	<5	10 (21.28%)	17 (36.17%)
CPRD GOLD	n (%)	0	0	0	0	0	0	0
Mucolytics								
APHM	n (%)	<5	0	0	0	0	<5	5 (10.42%)
CDW Bordeaux	n (%)	36 (67.92%)	22 (41.51%)	10 (18.87%)	33 (62.26%)	34 (64.15%)	36 (67.92%)	37 (69.81%)
IQVIA DA Germany	n (%)	23 (56.10%)	9 (21.95%)	<5	<5	9 (21.95%)	17 (41.46%)	24 (58.54%)
POLIMI	n (%)	25 (62.50%)	22 (55.00%)	22 (55.00%)	24 (60.00%)	24 (60.00%)	25 (62.50%)	28 (70.00%)
NLHR	n (%)	20 (42.55%)	20 (42.55%)	5 (10.64%)	10 (21.28%)	24 (51.06%)	31 (65.96%)	38 (80.85%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	35 (72.92%)	32 (66.67%)	29 (60.42%)	14 (29.17%)	14 (29.17%)	17 (35.42%)	26 (54.17%)
CDW Bordeaux	n (%)	25 (47.17%)	14 (26.42%)	6 (11.32%)	9 (16.98%)	12 (22.64%)	20 (37.74%)	27 (50.94%)
IQVIA DA Germany	n (%)	16 (39.02%)	12 (29.27%)	<5	0	11 (26.83%)	19 (46.34%)	24 (58.54%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
POLIMI	n (%)	23 (57.50%)	23 (57.50%)	19 (47.50%)	21 (52.50%)	21 (52.50%)	21 (52.50%)	21 (52.50%)
NLHR	n (%)	21 (44.68%)	19 (40.43%)	<5	7 (14.89%)	14 (29.79%)	23 (48.94%)	26 (55.32%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	17 (36.17%)	16 (34.04%)	11 (23.40%)	<5	<5	10 (21.28%)	16 (34.04%)
CDW Bordeaux	n (%)	8 (16.33%)	6 (12.24%)	6 (12.24%)	8 (16.33%)	8 (16.33%)	9 (18.37%)	9 (18.37%)
IQVIA DA Germany	n (%)	20 (50.00%)	13 (32.50%)	<5	<5	15 (37.50%)	23 (57.50%)	31 (77.50%)
POLIMI	n (%)	18 (45.00%)	18 (45.00%)	15 (37.50%)	17 (42.50%)	17 (42.50%)	17 (42.50%)	19 (47.50%)
NLHR	n (%)	<5	<5	-	<5	<5	<5	6 (12.77%)
CPRD GOLD	n (%)	0	0	-	0	0	0	0
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	20 (41.67%)	9 (18.75%)	<5	<5	<5	7 (14.58%)	10 (20.83%)
CDW Bordeaux	n (%)	35 (66.04%)	22 (41.51%)	10 (18.87%)	14 (26.42%)	16 (30.19%)	19 (35.85%)	25 (47.17%)
IQVIA DA Germany	n (%)	17 (41.46%)	9 (21.95%)	5 (12.20%)	<5	<5	10 (24.39%)	17 (41.46%)
POLIMI	n (%)	18 (45.00%)	16 (40.00%)	13 (32.50%)	12 (30.00%)	13 (32.50%)	13 (32.50%)	15 (37.50%)
NLHR	n (%)	6 (12.77%)	6 (12.77%)	0	<5	<5	11 (23.40%)	18 (38.30%)
CPRD GOLD	n (%)	<5	<5	0	0	<5	<5	<5
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	39 (97.50%)	39 (97.50%)	36 (90.00%)	32 (80.00%)	33 (82.50%)	35 (87.50%)	37 (92.50%)
NLHR	n (%)	25 (53.19%)	25 (53.19%)	<5	21 (44.68%)	33 (70.21%)	43 (91.49%)	46 (97.87%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S10. Frequency of supportive CF therapies use in individuals on ivacaftor and lumacaftor across different pre- and post-index windows, in paediatric population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	14 (50.00%)	13 (46.43%)	9 (32.14%)	<5	<5	6 (21.43%)	10 (35.71%)
CDW Bordeaux	n (%)	12 (35.29%)	8 (23.53%)	5 (14.71%)	5 (14.71%)	5 (14.71%)	10 (29.41%)	13 (38.24%)
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	6 (24.00%)	<5	0	<5	<5	6 (24.00%)	9 (36.00%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	<5	<5
CDW Bordeaux	n (%)	27 (79.41%)	18 (52.94%)	8 (23.53%)	23 (67.65%)	24 (70.59%)	26 (76.47%)	26 (76.47%)
IQVIA DA Germany	n (%)	<5	<5	0	0	<5	<5	<5
POLIMI	n (%)	9 (81.82%)	8 (72.73%)	8 (72.73%)	9 (81.82%)	9 (81.82%)	9 (81.82%)	9 (81.82%)
NLHR	n (%)	13 (52.00%)	13 (52.00%)	<5	<5	15 (60.00%)	16 (64.00%)	18 (72.00%)
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	22 (78.57%)	19 (67.86%)	19 (67.86%)	12 (42.86%)	12 (42.86%)	13 (46.43%)	20 (71.43%)
CDW Bordeaux	n (%)	20 (58.82%)	12 (35.29%)	<5	6 (17.65%)	9 (26.47%)	17 (50.00%)	23 (67.65%)
IQVIA DA Germany	n (%)	5 (83.33%)	5 (83.33%)	0	0	<5	<5	<5
POLIMI	n (%)	10 (90.91%)	10 (90.91%)	8 (72.73%)	9 (81.82%)	9 (81.82%)	9 (81.82%)	9 (81.82%)
NLHR	n (%)	11 (44.00%)	9 (36.00%)	0	<5	5 (20.00%)	8 (32.00%)	9 (36.00%)

Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	8 (29.63%)	7 (25.93%)	<5	0	0	<5	7 (25.93%)
CDW Bordeaux	n (%)	8 (24.24%)	6 (18.18%)	6 (18.18%)	7 (21.21%)	7 (21.21%)	8 (24.24%)	8 (24.24%)
IQVIA DA Germany	n (%)	<5	<5	0	0	<5	<5	<5
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	<5	<5	-	<5	<5	<5	5 (20.00%)
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	10 (35.71%)	<5	<5	<5	<5	<5	<5
CDW Bordeaux	n (%)	25 (73.53%)	16 (47.06%)	5 (14.71%)	7 (20.59%)	9 (26.47%)	12 (35.29%)	18 (52.94%)
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5
POLIMI	n (%)	7 (63.64%)	6 (54.55%)	5 (45.45%)	5 (45.45%)	5 (45.45%)	5 (45.45%)	5 (45.45%)
NLHR	n (%)	5 (20.00%)	5 (20.00%)	0	0	<5	5 (20.00%)	10 (40.00%)
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	11 (100.00%)	11 (100.00%)	9 (81.82%)	9 (81.82%)	9 (81.82%)	9 (81.82%)	10 (90.91%)
NLHR	n (%)	17 (68.00%)	17 (68.00%)	<5	10 (40.00%)	17 (68.00%)	22 (88.00%)	24 (96.00%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S11. Frequency of supportive CF therapies use in individuals on ivacaftor and lumacaftor across different pre- and post-index windows, in adult population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	14 (70.00%)	10 (50.00%)	9 (45.00%)	<5	<5	8 (40.00%)	11 (55.00%)
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	10 (28.57%)	6 (17.14%)	<5	<5	5 (14.29%)	8 (22.86%)	17 (48.57%)
POLIMI	n (%)	17 (58.62%)	15 (51.72%)	14 (48.28%)	19 (65.52%)	19 (65.52%)	19 (65.52%)	20 (68.97%)
NLHR	n (%)	<5	<5	<5	<5	<5	<5	8 (36.36%)
CPRD GOLD	n (%)	0	0	0	0	0	0	0
Mucolytics								
APHM	n (%)	<5	0	0	0	0	<5	<5
CDW Bordeaux	n (%)	9 (47.37%)	<5	<5	10 (52.63%)	10 (52.63%)	10 (52.63%)	11 (57.89%)
IQVIA DA Germany	n (%)	21 (60.00%)	8 (22.86%)	<5	<5	8 (22.86%)	15 (42.86%)	22 (62.86%)
POLIMI	n (%)	16 (55.17%)	14 (48.28%)	14 (48.28%)	15 (51.72%)	15 (51.72%)	16 (55.17%)	19 (65.52%)
NLHR	n (%)	7 (31.82%)	7 (31.82%)	<5	6 (27.27%)	9 (40.91%)	15 (68.18%)	20 (90.91%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	13 (65.00%)	13 (65.00%)	10 (50.00%)	<5	<5	<5	6 (30.00%)
CDW Bordeaux	n (%)	5 (26.32%)	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	11 (31.43%)	7 (20.00%)	<5	0	8 (22.86%)	15 (42.86%)	20 (57.14%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
POLIMI	n (%)	13 (44.83%)	13 (44.83%)	11 (37.93%)	12 (41.38%)	12 (41.38%)	12 (41.38%)	12 (41.38%)
NLHR	n (%)	10 (45.45%)	10 (45.45%)	<5	5 (22.73%)	9 (40.91%)	15 (68.18%)	17 (77.27%)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	9 (45.00%)	9 (45.00%)	7 (35.00%)	<5	<5	7 (35.00%)	9 (45.00%)
CDW Bordeaux	n (%)	0	0	0	<5	<5	<5	<5
IQVIA DA Germany	n (%)	17 (50.00%)	10 (29.41%)	<5	<5	13 (38.24%)	20 (58.82%)	28 (82.35%)
POLIMI	n (%)	15 (51.72%)	15 (51.72%)	13 (44.83%)	14 (48.28%)	14 (48.28%)	14 (48.28%)	16 (55.17%)
NLHR	n (%)	0	0	-	0	0	0	<5
CPRD GOLD	n (%)	0	0	-	0	0	0	0
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	10 (50.00%)	6 (30.00%)	<5	<5	<5	6 (30.00%)	6 (30.00%)
CDW Bordeaux	n (%)	10 (52.63%)	6 (31.58%)	5 (26.32%)	7 (36.84%)	7 (36.84%)	7 (36.84%)	7 (36.84%)
IQVIA DA Germany	n (%)	16 (45.71%)	8 (22.86%)	5 (14.29%)	<5	<5	9 (25.71%)	16 (45.71%)
POLIMI	n (%)	11 (37.93%)	10 (34.48%)	8 (27.59%)	7 (24.14%)	8 (27.59%)	8 (27.59%)	10 (34.48%)
NLHR	n (%)	<5	<5	0	<5	<5	6 (27.27%)	8 (36.36%)
CPRD GOLD	n (%)	<5	<5	0	0	<5	<5	<5
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	28 (96.55%)	28 (96.55%)	27 (93.10%)	23 (79.31%)	24 (82.76%)	26 (89.66%)	27 (93.10%)
NLHR	n (%)	8 (36.36%)	8 (36.36%)	<5	11 (50.00%)	16 (72.73%)	21 (95.45%)	22 (100.00%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S12. Frequency of supportive CF therapies use in individuals on ivacaftor and tezacaftor across different pre- and post-index windows, in the overall population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0
IQVIA DA Germany	n (%)	16 (43.24%)	13 (35.14%)	<5	<5	<5	7 (18.92%)	17 (45.95%)
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Mucolytics								
CDW Bordeaux	n (%)	<5	0	0	0	0	<5	<5
IQVIA DA Germany	n (%)	19 (51.35%)	12 (32.43%)	<5	<5	9 (24.32%)	13 (35.14%)	17 (45.95%)
NLHR	n (%)	<5	<5	0	<5	<5	<5	<5
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
CDW Bordeaux	n (%)	<5	0	0	0	0	0	0

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	22 (59.46%)	17 (45.95%)	<5	<5	9 (24.32%)	17 (45.95%)	20 (54.05%)
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	6 (100.00%)	5 (83.33%)	0	<5	5 (83.33%)	6 (100.00%)	6 (100.00%)
Bile acid preparations (usodeoxycholic acid)								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0
IQVIA DA Germany	n (%)	15 (46.88%)	11 (34.38%)	0	<5	7 (21.88%)	9 (28.12%)	16 (50.00%)
NLHR	n (%)	0	0	-	0	0	0	0
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0
IQVIA DA Germany	n (%)	15 (40.54%)	5 (13.51%)	0	<5	<5	7 (18.92%)	10 (27.03%)
NLHR	n (%)	<5	0	0	0	0	0	0
CPRD GOLD	n (%)	<5	0	0	0	0	0	0
Multienzymes (pancreatic enzymes)								
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	6 (100.00%)	5 (83.33%)	0	<5	6 (100.00%)	6 (100.00%)	6 (100.00%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S13. Frequency of supportive CF therapies use in individuals on ivacaftor and tezacaftor across different pre- and post-index windows, in paediatric population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0
Mucolytics								
CDW Bordeaux	n (%)	<5	0	0	0	0	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
CDW Bordeaux	n (%)	<5	0	0	0	0	0	0
Ursodeoxycholic acid (bile acid preparation)								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0
Aminoglycoside antibacterials (tobramycin)								
CDW Bordeaux	n (%)	0	0	0	0	0	0	0

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort.

Table S14. Frequency of supportive CF therapies use in individuals on ivacaftor and tezacaftor across different pre- and post-index windows, in adult population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
IQVIA DA Germany	n (%)	16 (43.24%)	13 (35.14%)	<5	<5	<5	7 (18.92%)	17 (45.95%)
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Mucolytics								
IQVIA DA Germany	n (%)	19 (51.35%)	12 (32.43%)	<5	<5	9 (24.32%)	13 (35.14%)	17 (45.95%)
NLHR	n (%)	<5	<5	0	<5	<5	<5	<5
CPRD GOLD	n (%)	<5	<5	0	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
IQVIA DA Germany	n (%)	22 (59.46%)	17 (45.95%)	<5	<5	9 (24.32%)	17 (45.95%)	20 (54.05%)
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	6 (100.00%)	5 (83.33%)	0	<5	5 (83.33%)	6 (100.00%)	6 (100.00%)
Ursodeoxycholic acid (bile acid preparation)								
IQVIA DA Germany	n (%)	15 (46.88%)	11 (34.38%)	0	<5	7 (21.88%)	9 (28.12%)	16 (50.00%)
NLHR	n (%)	0	0	-	0	0	0	0
CPRD GOLD	n (%)	<5	<5	-	<5	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
IQVIA DA Germany	n (%)	15 (40.54%)	5 (13.51%)	0	<5	<5	7 (18.92%)	10 (27.03%)
NLHR	n (%)	<5	0	0	0	0	0	0
CPRD GOLD	n (%)	<5	0	0	0	0	0	0
Multienzymes (pancreatic enzymes)								
NLHR	n (%)	<5	<5	0	0	<5	<5	<5
CPRD GOLD	n (%)	6 (100.00%)	5 (83.33%)	0	<5	6 (100.00%)	6 (100.00%)	6 (100.00%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S15. Frequency of supportive CF therapies use in individuals on ivacaftor, tezacaftor and elexacaftor across different pre- and post-index windows, in the overall population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	23 (74.19%)	15 (48.39%)	14 (45.16%)	<5	5 (16.13%)	7 (22.58%)	8 (25.81%)
CDW Bordeaux	n (%)	13 (46.43%)	8 (28.57%)	6 (21.43%)	8 (28.57%)	8 (28.57%)	8 (28.57%)	8 (28.57%)
IQVIA DA Germany	n (%)	25 (29.76%)	14 (16.67%)	<5	0	7 (8.33%)	12 (14.29%)	23 (27.38%)
POLIMI	n (%)	18 (90.00%)	14 (70.00%)	13 (65.00%)	14 (70.00%)	14 (70.00%)	14 (70.00%)	15 (75.00%)
NLHR	n (%)	81 (40.91%)	52 (26.26%)	<5	12 (6.06%)	30 (15.15%)	44 (22.22%)	46 (23.23%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
H12O	n (%)	29 (78.38%)	17 (45.95%)	8 (21.62%)	<5	<5	8 (21.62%)	13 (35.14%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	<5
CDW Bordeaux	n (%)	24 (85.71%)	13 (46.43%)	9 (32.14%)	16 (57.14%)	16 (57.14%)	16 (57.14%)	17 (60.71%)
IQVIA DA Germany	n (%)	46 (54.76%)	27 (32.14%)	<5	7 (8.33%)	12 (14.29%)	17 (20.24%)	26 (30.95%)
POLIMI	n (%)	9 (45.00%)	5 (25.00%)	<5	<5	<5	<5	<5
NLHR	n (%)	167 (84.34%)	136 (68.69%)	12 (6.06%)	40 (20.20%)	75 (37.88%)	111 (56.06%)	113 (57.07%)
H12O	n (%)	18 (48.65%)	8 (21.62%)	6 (16.22%)	<5	<5	<5	6 (16.22%)
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	21 (67.74%)	14 (45.16%)	9 (29.03%)	<5	<5	6 (19.35%)	8 (25.81%)
CDW Bordeaux	n (%)	21 (75.00%)	9 (32.14%)	<5	<5	<5	6 (21.43%)	9 (32.14%)
IQVIA DA Germany	n (%)	43 (51.19%)	30 (35.71%)	<5	<5	9 (10.71%)	23 (27.38%)	38 (45.24%)
POLIMI	n (%)	13 (65.00%)	7 (35.00%)	<5	<5	<5	<5	<5
NLHR	n (%)	156 (78.79%)	116 (58.59%)	<5	23 (11.62%)	58 (29.29%)	95 (47.98%)	100 (50.51%)
H12O	n (%)	24 (64.86%)	13 (35.14%)	8 (21.62%)	<5	6 (16.22%)	9 (24.32%)	10 (27.03%)
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	15 (53.57%)	11 (39.29%)	9 (32.14%)	<5	<5	<5	5 (17.86%)
CDW Bordeaux	n (%)	5 (18.52%)	5 (18.52%)	5 (18.52%)	<5	<5	<5	<5
IQVIA DA Germany	n (%)	42 (50.60%)	25 (30.12%)	<5	<5	14 (16.87%)	34 (40.96%)	40 (48.19%)
POLIMI	n (%)	10 (50.00%)	10 (50.00%)	10 (50.00%)	9 (45.00%)	9 (45.00%)	9 (45.00%)	9 (45.00%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
NLHR	n (%)	19 (9.69%)	14 (7.14%)	-	<5	9 (4.59%)	13 (6.63%)	13 (6.63%)
H12O	n (%)	14 (37.84%)	5 (13.51%)	<5	0	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	14 (45.16%)	<5	<5	<5	<5	<5	5 (16.13%)
CDW Bordeaux	n (%)	22 (78.57%)	8 (28.57%)	<5	<5	5 (17.86%)	6 (21.43%)	6 (21.43%)
IQVIA DA Germany	n (%)	44 (52.38%)	20 (23.81%)	<5	<5	9 (10.71%)	13 (15.48%)	21 (25.00%)
POLIMI	n (%)	8 (40.00%)	<5	<5	<5	<5	<5	<5
NLHR	n (%)	66 (33.33%)	33 (16.67%)	0	<5	12 (6.06%)	21 (10.61%)	21 (10.61%)
H12O	n (%)	28 (75.68%)	16 (43.24%)	8 (21.62%)	9 (24.32%)	11 (29.73%)	13 (35.14%)	14 (37.84%)
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	12 (60.00%)	12 (60.00%)	10 (50.00%)	9 (45.00%)	10 (50.00%)	10 (50.00%)	10 (50.00%)
NLHR	n (%)	138 (70.41%)	126 (64.29%)	14 (7.14%)	53 (27.04%)	101 (51.53%)	122 (62.24%)	127 (64.80%)
H12O	n (%)	32 (86.49%)	18 (48.65%)	10 (27.03%)	<5	6 (16.22%)	12 (32.43%)	16 (43.24%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S16. Frequency of supportive CF therapies use in individuals on ivacaftor, tezacaftor and elexacaftor across different pre- and post-index windows, in paediatric population, per data source, 2015–2024.

CDM name	Estimate name	Time window: Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	9 (69.23%)	5 (38.46%)	<5	0	<5	<5	<5
CDW Bordeaux	n (%)	8 (42.11%)	5 (26.32%)	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	0	0	0	0	0	0	<5
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	25 (37.31%)	13 (19.40%)	<5	5 (7.46%)	7 (10.45%)	9 (13.43%)	9 (13.43%)
H12O	n (%)	5 (71.43%)	<5	<5	0	<5	<5	<5
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	0
CDW Bordeaux	n (%)	17 (89.47%)	10 (52.63%)	7 (36.84%)	12 (63.16%)	12 (63.16%)	12 (63.16%)	13 (68.42%)
IQVIA DA Germany	n (%)	<5	<5	0	<5	<5	<5	<5
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	65 (97.01%)	60 (89.55%)	5 (7.46%)	21 (31.34%)	37 (55.22%)	49 (73.13%)	51 (76.12%)
H12O	n (%)	5 (71.43%)	<5	<5	<5	<5	<5	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	10 (76.92%)	8 (61.54%)	5 (38.46%)	<5	<5	<5	-
CDW Bordeaux	n (%)	15 (78.95%)	6 (31.58%)	<5	<5	<5	<5	6 (31.58%)
IQVIA DA Germany	n (%)	<5	<5	0	0	0	<5	<5

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	50 (74.63%)	31 (46.27%)	<5	<5	14 (20.90%)	24 (35.82%)	25 (37.31%)
H12O	n (%)	7 (100.00%)	5 (71.43%)	<5	<5	5 (71.43%)	5 (71.43%)	5 (71.43%)
Bile acid preparations (usodeoxycholic acid)								
APHM	n (%)	<5	<5	<5	0	0	0	0
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	<5	<5	0	<5	<5	<5	<5
POLIMI	n (%)	0	0	0	0	0	0	0
NLHR	n (%)	10 (14.93%)	8 (11.94%)	-	<5	5 (7.46%)	7 (10.45%)	7 (10.45%)
H12O	n (%)	<5	<5	<5	0	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	7 (53.85%)	<5	<5	0	<5	<5	<5
CDW Bordeaux	n (%)	15 (78.95%)	5 (26.32%)	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	0	0	0	0	0	0	0
POLIMI	n (%)	0	0	0	<5	<5	<5	<5
NLHR	n (%)	29 (43.28%)	8 (11.94%)	0	<5	<5	<5	<5
H12O	n (%)	5 (71.43%)	<5	<5	<5	<5	<5	<5
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	<5	<5	<5	<5	<5	<5	<5
NLHR	n (%)	56 (83.58%)	55 (82.09%)	5 (7.46%)	22 (32.84%)	48 (71.64%)	55 (82.09%)	56 (83.58%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
H12O	n (%)	5 (71.43%)	5 (71.43%)	5 (71.43%)	<5	<5	<5	<5

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S17. Frequency of supportive CF therapies use in individuals on ivacaftor, tezacaftor and elexacaftor across different pre- and post-index windows, in adult population, per data source, 2015–2024.

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
Proton pump inhibitors								
APHM	n (%)	14 (77.78%)	10 (55.56%)	10 (55.56%)	<5	<5	5 (27.78%)	6 (33.33%)
CDW Bordeaux	n (%)	5 (55.56%)	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	25 (32.05%)	14 (17.95%)	<5	0	7 (8.97%)	12 (15.38%)	22 (28.21%)
POLIMI	n (%)	16 (88.89%)	12 (66.67%)	11 (61.11%)	12 (66.67%)	12 (66.67%)	12 (66.67%)	13 (72.22%)
NLHR	n (%)	56 (42.75%)	39 (29.77%)	<5	7 (5.34%)	23 (17.56%)	35 (26.72%)	37 (28.24%)
H12O	n (%)	24 (80.00%)	13 (43.33%)	<5	<5	<5	7 (23.33%)	11 (36.67%)
Mucolytics								
APHM	n (%)	<5	0	0	0	0	0	<5
CDW Bordeaux	n (%)	7 (77.78%)	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	44 (56.41%)	26 (33.33%)	<5	6 (7.69%)	11 (14.10%)	15 (19.23%)	24 (30.77%)
POLIMI	n (%)	7 (38.89%)	<5	<5	<5	<5	<5	<5

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
NLHR	n (%)	102 (77.86%)	76 (58.02%)	7 (5.34%)	19 (14.50%)	38 (29.01%)	62 (47.33%)	62 (47.33%)
H12O	n (%)	13 (43.33%)	<5	<5	0	0	0	<5
Selective beta-2-adrenoreceptor agonists (salbutamol)								
APHM	n (%)	11 (61.11%)	6 (33.33%)	<5	<5	<5	<5	5 (27.78%)
CDW Bordeaux	n (%)	6 (66.67%)	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	40 (51.28%)	29 (37.18%)	<5	<5	9 (11.54%)	22 (28.21%)	36 (46.15%)
POLIMI	n (%)	11 (61.11%)	5 (27.78%)	<5	<5	<5	<5	<5
NLHR	n (%)	106 (80.92%)	85 (64.89%)	<5	19 (14.50%)	44 (33.59%)	71 (54.20%)	75 (57.25%)
H12O	n (%)	17 (56.67%)	8 (26.67%)	5 (16.67%)	<5	<5	<5	5 (16.67%)
Ursodeoxycholic acid (bile acid preparation)								
APHM	n (%)	11 (68.75%)	10 (62.50%)	8 (50.00%)	<5	<5	<5	5 (31.25%)
CDW Bordeaux	n (%)	<5	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	40 (51.95%)	24 (31.17%)	<5	<5	12 (15.58%)	32 (41.56%)	36 (46.75%)
POLIMI	n (%)	10 (55.56%)	10 (55.56%)	10 (55.56%)	9 (50.00%)	9 (50.00%)	9 (50.00%)	9 (50.00%)
NLHR	n (%)	9 (6.98%)	6 (4.65%)	-	<5	<5	6 (4.65%)	6 (4.65%)
H12O	n (%)	12 (40.00%)	<5	<5	0	<5	<5	<5
Aminoglycoside antibacterials (tobramycin)								
APHM	n (%)	7 (38.89%)	<5	<5	<5	<5	<5	<5
CDW Bordeaux	n (%)	7 (77.78%)	<5	<5	<5	<5	<5	<5
IQVIA DA Germany	n (%)	44 (56.41%)	20 (25.64%)	<5	<5	9 (11.54%)	13 (16.67%)	21 (26.92%)

CDM name	Estimate name	Time window						
		Any time prior ID (-Inf to 0)	One year prior ID (-365 to 0)	Index date (ID) (0 to 0)	30 days post ID (1 to 30)	90 days post ID (1 to 90)	One year post ID (1 to 365)	Any time post ID (1 to Inf)
POLIMI	n (%)	8 (44.44%)	<5	<5	<5	<5	<5	<5
NLHR	n (%)	37 (28.24%)	25 (19.08%)	0	<5	9 (6.87%)	17 (12.98%)	17 (12.98%)
H12O	n (%)	23 (76.67%)	14 (46.67%)	6 (20.00%)	7 (23.33%)	9 (30.00%)	11 (36.67%)	12 (40.00%)
Multienzymes (pancreatic enzymes)								
POLIMI	n (%)	11 (61.11%)	11 (61.11%)	9 (50.00%)	8 (44.44%)	9 (50.00%)	9 (50.00%)	9 (50.00%)
NLHR	n (%)	82 (63.57%)	71 (55.04%)	9 (6.98%)	31 (24.03%)	53 (41.09%)	67 (51.94%)	71 (55.04%)
H12O	n (%)	27 (90.00%)	13 (43.33%)	5 (16.67%)	<5	<5	10 (33.33%)	13 (43.33%)

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, ID = index date, n (%) = number of individuals (percentage of cohort), "-" indicates absence of data for the specified time window.

Table S18. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulator ivacaftor, overall and stratified by age, 2015–2024.

Level	Variable name	Estimate name	CDM name						
			APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
Overall	Number of subjects	N	29	18	122	63	208	55	11
	Number of exposures	Median [q25–q75]	1 [1–2]	5 [2–8]	12 [4–32]	9 [2–14]	9 [6–12]	1 [1–2]	1 [1–1]
		Range	1 to 6	1 to 25	1 to 71	1 to 55	1 to 33	1 to 6	1 to 1
	Days exposed	Median [q25–q75]	5 [3–13]	4 [2–11]	556 [178–1,371]	9 [6–16]	500 [337–542]	366 [104–440]	28 [1–28]
		Range	1 to 138	1 to 97	28 to 2,709	1 to 147	15 to 2,134	2 to 1,500	1 to 28
	Cumulative dose, milligram	Median [q25–q75]	750 [300–1,800]	-	75,600 [26,250–196,350]	-	37,800 [18,900–44,100]	-	4,200 [600–8,400]
		Range	75 to 15,300	-	2,100 to 598,050	-	1,330 to 356,116	-	150 to 8,400
< 18	Number of subjects	N	15	6	7	12	65	10	<5
	Number of exposures	Median [q25–q75]	1 [1–2]	6 [3–17]	5 [1–9]	2 [1–2]	9 [6–11]	1 [1–1]	-
		Range	1 to 6	2 to 25	1 to 15	1 to 4	2 to 20	1 to 6	-
	Days exposed	Median [q25–q75]	3 [2–8]	6 [3–61]	286 [28–370]	6 [4–7]	447 [358–530]	16 [6–28]	-
		Range	1 to 129	2 to 97	28 to 516	1 to 16	57 to 2,063	2 to 155	-
	Cumulative dose, milligram	Median [q25–q75]	300 [188–900]	-	14,700 [3,150–47,250]	-	31,500 [11,550–40,584]	-	-
		Range	75 to 15,300	-	2,100 to 63,000	-	1,330 to 306,600	-	-
>= 18	Number of subjects	N	14	12	115	51	143	45	10
	Number of exposures	Median [q25–q75]	1 [1–2]	4 [2–7]	13 [5–32]	11 [4–16]	9 [6–12]	1 [1–2]	1 [1–1]
		Range	1 to 4	1 to 21	1 to 71	1 to 55	1 to 33	1 to 5	1 to 1

Level	Variable name	Estimate name	CDM name						
			APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O	CPRD GOLD
	Days exposed	Median [q25–q75]	7 [5–18]	4 [2–8]	679 [206–1,445]	11 [7–22]	524 [332–546]	366 [366–540]	28 [1–28]
		Range	1 to 138	1 to 51	28 to 2,709	1 to 147	15 to 2,134	8 to 1,500	1 to 28
	Cumulative dose, milligram	Median [q25–q75]	975 [638–1,913]	-	88,200 [29,400–205,950]	-	38,959 [27,660–44,100]	-	4,200 [375–7,350]
		Range	150 to 4,200	-	2,100 to 598,050	-	2,100 to 356,116	-	150 to 8,400

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Table S19. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulator ivacaftor and lumacaftor, overall and stratified by age, 2015–2024.

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	CPRD GOLD
Overall	Number of subjects	N	Overall	48	53	41	40	47	<5
	Number of exposures	Median [q25–q75]	Ivacaftor, lumacaftor	1 [1–2]	4 [2–10]	8 [1–12]	5 [2–20]	16 [10–26]	-
		Range	Ivacaftor, lumacaftor	1 to 7	1 to 222	1 to 30	1 to 37	1 to 47	-
	Days exposed	Median [q25–q75]	Ivacaftor, lumacaftor	5 [3–10]	3 [2–8]	377 [78–701]	11 [7–15]	1,317 [452–1,658]	-
		Range	Ivacaftor, lumacaftor	2 to 116	1 to 725	28 to 1,378	1 to 37	57 to 1,758	-
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	2,034 [1,500–3,500]	-	0 [0–0]	-	-	-
		Range	Ivacaftor	500 to 17,750	-	0 to 420,000	-	-	-

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	CPRD GOLD
		Median [q25–q75]	Lumacaftor	3,200 [2,375–5,225]	-	0 [0–0]	-	-	-
		Range	Lumacaftor	500 to 28,400	-	0 to 336,000	-	-	-
< 18	Number of subjects	N	Overall	28	34	6	11	25	-
	Number of exposures	Median [q25–q75]	Ivacaftor, lumacaftor	1 [1–2]	4 [2–10]	11 [2–25]	3 [2–4]	14 [10–20]	-
		Range	Ivacaftor, lumacaftor	1 to 7	1 to 222	1 to 30	1 to 26	1 to 47	-
	Days exposed	Median [q25–q75]	Ivacaftor, lumacaftor	5 [3–13]	3 [2–10]	506 [52–929]	13 [10–15]	1,159 [428–1,655]	-
		Range	Ivacaftor, lumacaftor	2 to 116	1 to 725	30 to 998	5 to 22	57 to 1,737	-
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	2,034 [1,500–3,500]	-	24,500 [7,000–52,500]	-	-	-
		Range	Ivacaftor	625 to 17,750	-	0 to 420,000	-	-	-
		Median [q25–q75]	Lumacaftor	3,200 [1,638–4,875]	-	19,600 [5,600–42,000]	-	-	-
		Range	Lumacaftor	500 to 28,400	-	0 to 336,000	-	-	-
>= 18	Number of subjects	N	Overall	20	19	35	29	22	<5
	Number of exposures	Median [q25–q75]	Ivacaftor, lumacaftor	1 [1–1]	6 [3–9]	8 [2–10]	10 [3–22]	24 [11–32]	-
		Range	Ivacaftor, lumacaftor	1 to 3	1 to 40	1 to 20	1 to 37	2 to 42	-
	Days exposed	Median [q25–q75]	Ivacaftor, lumacaftor	5 [4–8]	4 [2–6]	377 [81–677]	9 [6–13]	1,543 [944–1,674]	-
		Range	Ivacaftor, lumacaftor	2 to 104	1 to 110	28 to 1,378	1 to 37	104 to 1,758	-
	Cumulative dose milligram	Median [q25–q75]	Ivacaftor	2,250 [2,000–3,625]	-	0 [0–0]	-	-	-

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	CPRD GOLD
		Range	Ivacaftor	500 to 10,000	-	0 to 28,000	-	-	-
		Median [q25–q75]	Lumacaftor	3,600 [3,200–5,800]	-	0 [0–0]	-	-	-
		Range	Lumacaftor	800 to 16,000	-	0 to 22,400	-	-	-

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Table S20. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulator ivacaftor and tezacaftor, overall and stratified by age, 2015–2024.

Level	Variable name	Estimate name	Additional level	CDM name*			
				CDW Bordeaux	IQVIA DA Germany	NLHR	CPRD GOLD
Overall	Number of subjects	N	Overall	<5	37	<5	6
	Number of exposures	Median [q25–q75]	Ivacaftor, tezacaftor	-	5 [1–10]	-	1 [1–1]
		Range	Ivacaftor, tezacaftor	-	1 to 14	-	1 to 1
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor	-	338 [84–613]	-	1 [1–1]
		Range	Ivacaftor, tezacaftor	-	28 to 1,396	-	1 to 1
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	-	46,200 [8,400–79,800]	-	600 [150–3,413]
		Range	Ivacaftor	-	4,200 to 159,600	-	150 to 8,400
		Median [q25–q75]	Tezacaftor	-	30,800 [5,600–53,200]	-	400 [100–2,275]
		Range	Tezacaftor	-	2,800 to 106,400	-	100 to 5,600
< 18	Number of subjects	N	Overall	<5	-	-	-
	Number of exposures	Median [q25–q75]	Ivacaftor, tezacaftor	-	-	-	-
		Range	Ivacaftor, tezacaftor	-	-	-	-
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor	-	-	-	-
		Range	Ivacaftor, tezacaftor	-	-	-	-
>= 18	Number of subjects	N	Overall	-	37	<5	6
	Number of exposures	Median [q25–q75]	Ivacaftor, tezacaftor	-	5 [1–10]	-	1 [1–1]
		Range	Ivacaftor, tezacaftor	-	1 to 14	-	1 to 1
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor	-	338 [84–613]	-	1 [1–1]
		Range	Ivacaftor, tezacaftor	-	28 to 1,396	-	1 to 1
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	-	46,200 [8,400–79,800]	-	600 [150–3,413]
		Range	Ivacaftor	-	4,200 to 159,600	-	150 to 8,400

Level	Variable name	Estimate name	Additional level	CDM name*			
				CDW Bordeaux	IQVIA DA Germany	NLHR	CPRD GOLD
		Median [q25–q75]	Tezacaftor	-	30,800 [5,600–53,200]	-	400 [100–2,275]
		Range	Tezacaftor	-	2,800 to 106,400	-	100 to 5,600

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Table S21. Treatment duration, number of exposure episodes, and cumulative doses of CFTR modulator ivacaftor, tezacaftor and elexacaftor, overall and stratified by age, 2015–2024.

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O
Overall	Number subjects	N	Overall	31	28	84	20	198	37
	Number exposures	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	1 [1–2]	7 [4–10]	9 [3–16]	6 [3–9]	9 [7–12]	1 [1–2]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 9	1 to 71	1 to 28	1 to 43	1 to 24	1 to 5
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	6 [3–16]	5 [3–9]	647 [172–1,293]	8 [5–11]	538 [426–551]	366 [31–540]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 138	1 to 153	19 to 1,588	1 to 47	42 to 1,003	2 to 964
	Cumulative dose milligram	Median [q25–q75]	Ivacaftor	750 [338–1,425]	-	0 [0–15,750]	-	-	-
		Range	Ivacaftor	75 to 15,300	-	0 to 151,200	-	-	-
		Median [q25–q75]	Tezacaftor	500 [225–950]	-	0 [0–10,500]	-	-	-
		Range	Tezacaftor	50 to 10,200	-	0 to 100,800	-	-	-
		Median [q25–q75]	Elexacaftor	1,000 [450–1,900]	-	0 [0–21,000]	-	-	-
		Range	Elexacaftor	100 to 20,400	-	0 to 201,600	-	-	-
< 18	Number of subjects	N	overall	13	19	6	<5	67	7
	Number of exposures	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	1 [1–1]	7 [4–10]	4 [1–8]	-	8 [6–11]	1 [1–2]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 4	1 to 26	1 to 22	-	1 to 24	1 to 5

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	3 [2–9]	5 [4–10]	183 [28–368]	-	483 [405–538]	7 [4–30]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 129	1 to 79	28 to 974	-	78 to 1,003	2 to 155
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	375 [150–900]	-	0 [0–0]	-	-	-
		Range	Ivacaftor	75 to 15,300	-	0 to 0	-	-	-
		Median [q25–q75]	Tezacaftor	250 [100–600]	-	0 [0–0]	-	-	-
		Range	Tezacaftor	50 to 10,200	-	0 to 0	-	-	-
		Median [q25–q75]	Elexacaftor	500 [200–1,200]	-	0 [0–0]	-	-	-
		Range	Elexacaftor	100 to 20,400	-	0 to 0	-	-	-
>= 18	Number of subjects	N	overall	18	9	78	18	131	30
	Number of exposures	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	1 [1–2]	6 [5–8]	10 [3–16]	6 [3–10]	9 [7–12]	2 [1–2]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 9	1 to 71	1 to 28	1 to 43	1 to 21	1 to 5
	Days exposed	Median [q25–q75]	Ivacaftor, tezacaftor, elexacaftor	7 [5–18]	6 [3–7]	693 [227–1,369]	7 [4–9]	541 [454–552]	366 [344–686]
		Range	Ivacaftor, tezacaftor, elexacaftor	1 to 138	1 to 153	19 to 1,588	1 to 47	42 to 700	8 to 964
	Cumulative dose, milligram	Median [q25–q75]	Ivacaftor	938 [600–1,800]	-	0 [0–25,200]	-	-	-
		Range	Ivacaftor	150 to 15,075	-	0 to 151,200	-	-	-

Level	Variable name	Estimate name	Additional level	CDM name*					
				APHM	CDW Bordeaux	IQVIA DA Germany	POLIMI	NLHR	H12O
		Median [q25–q75]	Tezacaftor	625 [400–1,200]	-	0 [0–16,800]	-	-	-
		Range	Tezacaftor	100 to 10,050	-	0 to 100,800	-	-	-
		Median [q25–q75]	Elexacaftor	1,250 [800–2,400]	-	0 [0–33,600]	-	-	-
		Range	Elexacaftor	200 to 20,100	-	0 to 201,600	-	-	-

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, q25–q75 = 25th and 75th percentiles (interquartile range), range = minimum and maximum observed values. Cumulative dose is calculated for available drug components. "-" indicates data not available in the data source. *Data from CPRD GOLD are not presented in this table because ivacaftor, tezacaftor, and elexacaftor are not available in this data source.

Table S22. Incidence rate of pre-specified adverse event anxiety in CFTR modulator treated individuals (per active ingredient) in the overall population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Ivacaftor					
APHM	29	0	0	0	0; 8,867.50
CDW Bordeaux	15	<5	0	NA	NA
IQVIA DA Germany	121	0	51	0	0; 72.64
POLIMI	63	0	2	0	0; 2,008.10
NLHR	197	<5	80	NA	NA
H12O	52	0	53	0	0; 69.75
CPRD GOLD	11	0	1	0	0; 6,731.53
Ivacaftor and lumacaftor					
APHM	48	0	1	0	0; 3163.70
CDW Bordeaux	49	<5	0	NA	NA
IQVIA DA Germany	40	0	25	0	0; 147.35
POLIMI	40	0	1	0	0; 3,247.25
NLHR	43	<5	107	NA	NA
CPRD GOLD	NA	0	NA	0	0; 1,229,626.48
Ivacaftor and tezacaftor					
CDW Bordeaux	NA	0	NA	0	0; 1,229,626.48
IQVIA DA Germany	36	0	20	0	0; 187.40
NLHR	NA	0	NA	0	0; 1,625.06
CPRD GOLD	6	0	0	0	0; 230,554.97
Ivacaftor, tezacaftor, and elexacaftor					
APHM	31	0	1	0	0; 4,918.51

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
CDW Bordeaux	26	<5	0	NA	NA
IQVIA DA Germany	81	<5	69	NA	NA
POLIMI	20	0	1	0	0; 6,540.57
NLHR	187	7	230	30.38	12.21; 62.59
H12O	35	0	28	0	0; 130.02

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

Table S23. Incidence rate of pre-specified adverse event cataract in CFTR modulator treated individuals (per active ingredient) in the overall population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Ivacaftor					
APHM	29	0	0	0	0; 8,867.50
CDW Bordeaux	18	0	0	0	0; 13,463.06
IQVIA DA Germany	122	0	52	0	0; 70.98
POLIMI	63	0	2	0	0; 2,008.10
NLHR	205	<5	81	NA	NA
H12O	55	0	55	0	0; 67.15
CPRD GOLD	11	0	1	0	0; 6,731.53
Ivacaftor and lumacaftor					
APHM	48	0	1	0	0; 3,163.70
CDW Bordeaux	53	0	1	0	0; 6,575.54
IQVIA DA Germany	41	0	26	0	0; 143.81
POLIMI	40	0	1	0	0; 3,247.25

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
NLHR	47	0	126	0	0; 29.36
CPRD GOLD	NA	0	NA	0	0; 1,229,626.48
Ivacaftor and tezacaftor					
CDW Bordeaux	NA	0	NA	0	0; 1,229,626.48
IQVIA DA Germany	37	0	20	0	0; 186.67
NLHR	NA	0	NA	0	0; 1,625.06
CPRD GOLD	6	0	0	0	0; 230,554.97
Ivacaftor, tezacaftor, and elexacaftor					
APHM	31	0	1	0	0; 4,918.51
CDW Bordeaux	28	0	0	0	0; 7,407.39
IQVIA DA Germany	84	0	71	0	0; 52.02
POLIMI	20	0	1	0	0; 6,540.57
NLHR	196	<5	243	NA	NA
H12O	37	0	30	0	0; 121.44

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

Table S24. Incidence rate of pre-specified adverse event depression in CFTR modulator treated individuals (per active ingredient) in the overall population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PY	95% CI (lower; upper CI)
Ivacaftor					
APHM	29	0	0	0	0; 8,867.50
CDW Bordeaux	17	0	0	0	0; 17,237.75
IQVIA DA Germany	122	0	52	0	0; 70.98
POLIMI	63	0	2	0	0; 2,008.10
NLHR	202	0	85	0	0; 43.64
H12O	51	<5	48	NA	NA
CPRD GOLD	11	0	1	0	0; 6,731.53
Ivacaftor and lumacaftor					
APHM	48	0	1	0	0; 3,163.70
CDW Bordeaux	53	0	1	0	0; 6,575.54
IQVIA DA Germany	41	0	26	0	0; 143.81
POLIMI	40	0	1	0	0; 3,247.25
NLHR	47	0	126	0	0; 29.36
CPRD GOLD	NA	0	NA	0	0; 1,229,626.48
Ivacaftor and tezacaftor					
CDW Bordeaux	NA	0	NA	0	0; 1,229,626.48
IQVIA DA Germany	36	0	20	0	0; 187.40
NLHR	NA	0	NA	0	0; 1625.06
CPRD GOLD	6	0	0	0	0; 230,554.97
Ivacaftor, tezacaftor, and elexacaftor					
APHM	30	0	1	0	0; 5,640.49

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PY	95% CI (lower; upper CI)
CDW Bordeaux	28	0	0	0	0; 7,407.39
IQVIA DA Germany	82	0	71	0	0; 52.11
POLIMI	20	0	1	0	0; 6,540.57
NLHR	191	0	238	0	0; 15.48
H12O	34	<5	28	NA	NA; NA

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

Table S25. Incidence rate of pre-specified adverse event haemoptysis in CFTR modulator treated individuals (per active ingredient) in the overall population during the study period, per data source.

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Ivacaftor					
APHM	28	<5	0	NA	NA
CDW Bordeaux	16	<5	0	NA	NA
IQVIA DA Germany	122	0	52	0	0; 70.98
POLIMI	63	<5	2	NA	NA
NLHR	207	<5	85	NA	NA
H12O	51	0	52	0	0; 71.07
CPRD GOLD	11	0	1	0	0; 6,731.53
Ivacaftor and lumacaftor					
APHM	47	<5	1	NA	NA
CDW Bordeaux	50	<5	1	NA	NA
IQVIA DA Germany	41	0	26	0	0; 143.81
POLIMI	37	0	1	0	0; 3,564.13

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
NLHR	47	<5	121	NA	NA
CPRD GOLD	NA	0	NA	0	0; 1,229,626.48
Ivacaftor and tezacaftor					
CDW Bordeaux	NA	0	NA	0	0; 1,229,626.48
IQVIA DA Germany	37	0	20	0	0; 186.67
NLHR	NA	<5	NA	NA	NA
CPRD GOLD	6	0	0	0	0; 230,554.97
Ivacaftor, tezacaftor, and elexacaftor					
APHM	28	<5	1	NA	NA
CDW Bordeaux	26	<5	0	NA	NA
IQVIA DA Germany	84	0	71	0	0; 52.02
POLIMI	20	<5	1	NA	NA
NLHR	197	0	246	0	0; 15.02
H12O	34	0	29	0	0; 125.78

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

Table S26. Incidence rate of pulmonary exacerbation in CFTR modulator treated individuals (per active ingredient) in the overall population, per data source.

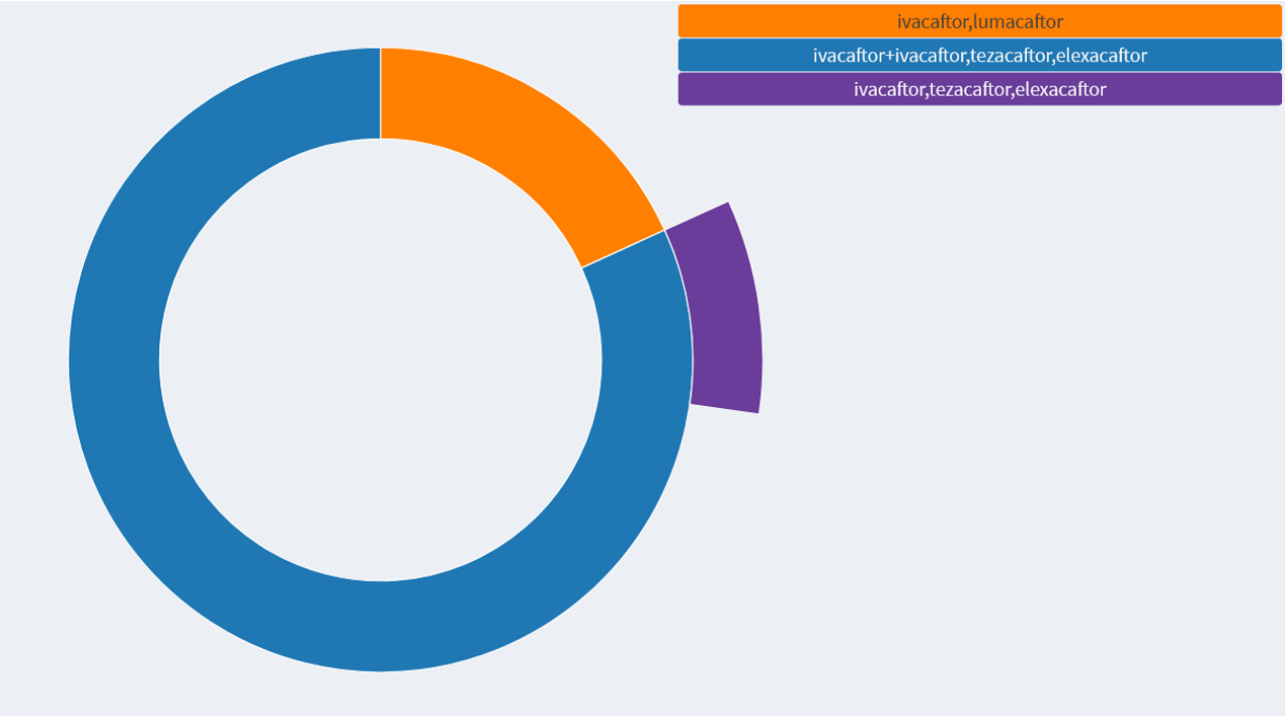
Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
Ivacaftor – One year post initiation					
APHM	16	7	0	NA	NA
CDW Bordeaux	8	5	0	NA	NA
IQVIA DA Germany	121	0	47	0	0; 78.49
POLIMI	43	30	0	NA	NA
NLHR	200	9	64	140.60	64.29; 266.83
H12O	55	<5	37	NA	NA
CPRD GOLD	11	0	1	0	0; 6,731.53
Ivacaftor – Two-year post initiation					
APHM	25	22	0	NA	NA
CDW Bordeaux	22	19	0	NA	NA
IQVIA DA Germany	8	0	3	0	0; 1,348.77
POLIMI	25	23	0	NA	NA
NLHR	21	<5	8	NA	NA
H12O	12	0	8	0	0; 443.06
CPRD GOLD	6	0	0	0	0; 230,554.97
Ivacaftor and lumacaftor – One year post initiation					
APHM	7	<5	0	NA	NA
CDW Bordeaux		0		0	0
IQVIA DA Germany	40	<5	15	NA	NA
POLIMI		<5		NA	NA
NLHR	33	<5	28	NA	NA
H12O	59	5	38	131.05	42.55; 305.84

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
CPRD GOLD		0		0	0
Ivacaftor and lumacaftor – Two-year post initiation					
APHM	14	14	0	NA	NA
CDW Bordeaux	11	9	0	NA	NA
IQVIA DA Germany	8	0	6	0	0; 612.67
POLIMI	9	8	0	NA	NA
NLHR	192	18	164	109.59	64.95; 173.20
H12O	13	0	8	0	0; 442.63
CPRD GOLD		0		0	0; 47,907.53
Ivacaftor and tezacaftor – One year post initiation					
APHM	19	9	0	NA	NA
CDW Bordeaux	5	<5	0	NA	NA
IQVIA DA Germany	37	0	16	0	0; 237.67
POLIMI	15	10	0	NA	NA
NLHR		0		0	0; 2,041.44
H12O	37	5	21	237.36	77.07; 553.92
CPRD GOLD		0		0	0; 1,229,626.48
Ivacaftor and tezacaftor – Two-year post initiation					
APHM	45	31	0	NA	NA
CDW Bordeaux	35	27	0	NA	NA
IQVIA DA Germany	7	0	4	0	0; 869.81
POLIMI	69	53	1	79,939.67	59,880.30; 104,563.05
NLHR	46	7	35	197.62	79.45; 407.17
H12O	8	0	5	0	0; 748.56

Data source	Number of persons	Number of events	Person years (PYs)	Incidence per 1,000 PYs	95% CI (lower; upper CI)
CPRD GOLD	13	0	1	0	0; 6,670.67
Ivacaftor, tezacaftor, and elexacaftor – One year post initiation					
APHM	7	<5	0	NA	NA
CDW Bordeaux		<5		NA	NA
IQVIA DA Germany	83	0	46	0	0; 81.06
POLIMI		<5		NA	NA
NLHR	154	9	60	148.82	68.05; 282.51
H12O	10	<5	0	NA	NA
CPRD GOLD	10	0	0	0	0; 7,832.02
Ivacaftor, tezacaftor, and elexacaftor – Two year post initiation					
APHM	21	15	0	NA	NA
CDW Bordeaux	15	10	0	NA	NA
IQVIA DA Germany	28	0	16	0	0; 229.69
POLIMI	13	9	0	NA	NA
NLHR	264	28	218	128.32	85.27; 185.46
H12O	7	<5	0	NA	NA
CPRD GOLD	6	0	0	0	0; 230,554.97

APHM = Assistance Publique – Hôpitaux de Marseille, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IQVIA DA Germany = IQVIA Disease Analyzer Germany, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NLHR = Norwegian Linked Health Registry data, H12O = Hospital Universitario 12 de Octubre, CPRD GOLD = Clinical Practice Research Datalink GOLD, NA = not applicable, PYs = person years, CI = confidence interval.

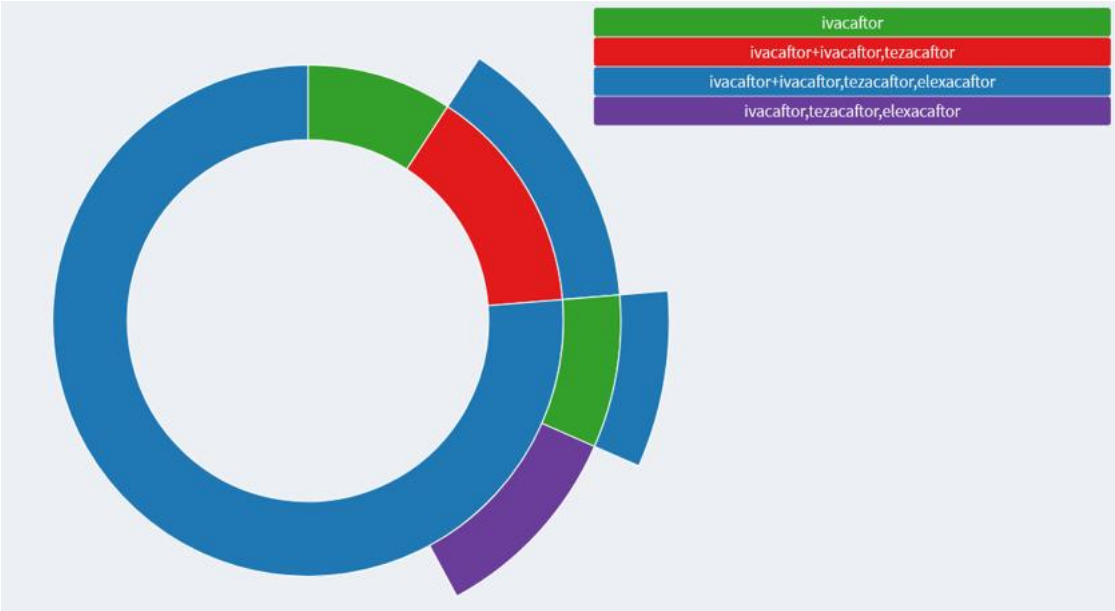
ANNEX III: Supplementary Figures



	Pathway	Combination	Line	Percentage
1	ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	1	81.82%
2	ivacaftor,lumacaftor	ivacaftor,lumacaftor	1	18.18%
3	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	2	9.09%

Figure S1. Sunburst plot of CFTR treatment in paediatric population in NLHR.

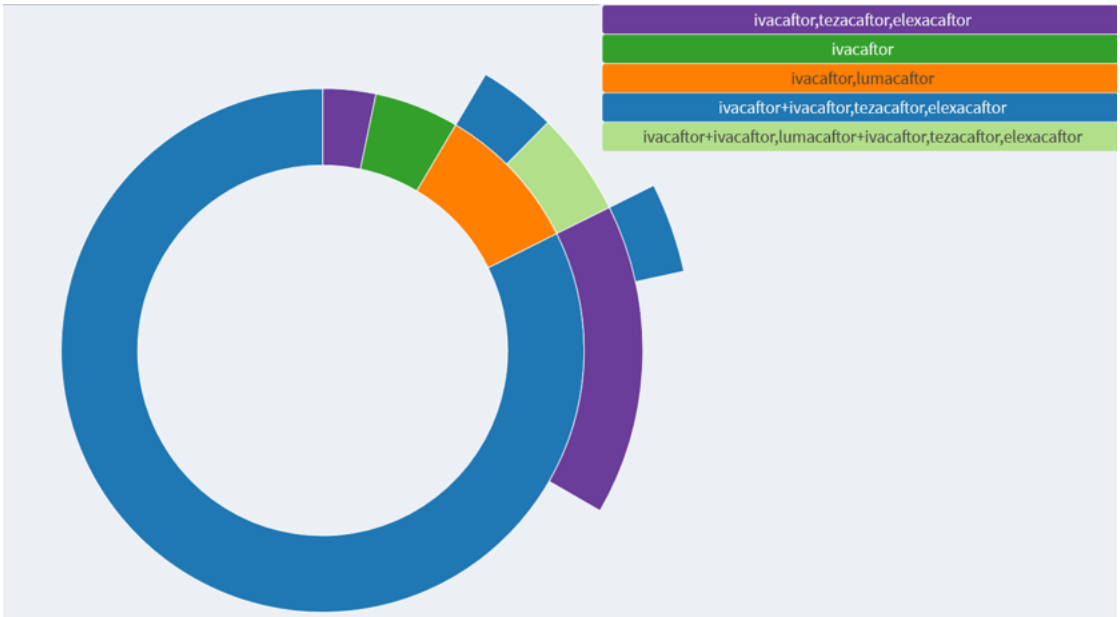
The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments, and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific CFTR modulator regimens as shown in the legend. The accompanying table provides detailed counts and percentages for each pathway.
Treatment pathways were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort that initiated that drug/drug combination.



	Pathway	Combination	Line	Percentage
1	ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	1	76.32%
2	ivacaftor+ivacaftor,tezacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor	1	14.47%
2	ivacaftor+ivacaftor,tezacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	2	14.47%
3	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	2	10.53%
4	ivacaftor	ivacaftor	1	9.21%
5	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor	2	7.89%
5	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	3	7.89%

Figure S2. Sunburst plot of CFTR treatment in the adult population in in IQVIA DA Germany.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments, and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific CFTR modulator regimens as shown in the legend. The accompanying table provides detailed counts and percentages for each pathway.
Treatment pathways were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort that initiated that drug/drug combination.



	Pathway	Combination	Line	Percentage
1	ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	1	82.35%
2	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	2	15.69%
3	ivacaftor	ivacaftor	1	5.23%
4	ivacaftor,lumacaftor-ivacaftor+ivacaftor,lumacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor,lumacaftor	1	9.15%
4	ivacaftor,lumacaftor-ivacaftor+ivacaftor,lumacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,lumacaftor+ivacaftor,tezacaftor,elexacaftor	2	5.23%
5	ivacaftor+ivacaftor,tezacaftor,elexacaftor-ivacaftor,tezacaftor,elexacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	3	3.92%
6	ivacaftor,lumacaftor-ivacaftor+ivacaftor,tezacaftor,elexacaftor	ivacaftor+ivacaftor,tezacaftor,elexacaftor	2	3.92%
7	ivacaftor,tezacaftor,elexacaftor	ivacaftor,tezacaftor,elexacaftor	1	3.27%

Figure S3. Sunburst plot of CFTR treatment in the adult population in NLHR.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments, and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific CFTR modulator regimens as shown in the legend. The accompanying table provides detailed counts and percentages for each pathway.
Treatment pathways were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort that initiated that drug/drug combination.