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Quantitative Safety & Epidemiology

QVA149 / Indacaterol / Glycopyrronium bromide

Non-interventional Final Study Report
CQVA149A2401

Multinational, multi-database drug utilization study of indacaterol/glycopyrronium bromide in Europe

Redacted Report

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Product reference	QVA149
Procedure number	EMEA/H/C/002679 EMEA/H/C/003755 EMEA/H/C/003875
Marketing authorization holder	[redacted]
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Research question and objectives	To estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the risk management plan (RMP)
Country(-ies) of study	United Kingdom, Denmark, Italy, The Netherlands, Spain
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	[redacted]
MAH contact person	[redacted]

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1 Abstract

Title

Multinational, multi-database drug utilization study of indacaterol/glycopyrronium bromide in Europe

Date of abstract:

05 November 2017

Name and affiliation of main author:

[redacted]

Keywords

Chronic obstructive pulmonary disease, glycopyrronium bromide, long-acting muscarinic antagonist, indacaterol, drug utilization

Rationale and background

Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered in the EU as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered in the EU as Seebri® Breezhaler® and related products). It is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). QVA149 has been approved by the European Commission on September 19th 2013. In the context of the QVA149 marketing authorization application, the Committee for Medicinal Products for Human Use (CHMP) recommended conditions for marketing authorization and product information and suggested to conduct a post-authorization drug utilization study to estimate the subpopulation with cardiovascular comorbidity, to identify patient groups with missing information as per the risk management plan (RMP) and to evaluate off-label use.

Research question and objectives

Primary objectives

1. To determine the proportion of patients using QVA149 who do not meet the criteria specified in the QVA149 label ('off-label use') i.e., use of QVA149 in patients younger than 18 years or in patients without a diagnosis of COPD or in patients with asthma/asthma and COPD without concomitant use of inhaled corticosteroids (ICS)
2. To determine the proportion of patients using QVA149 who have missing information as per RMP or high risk treatment conditions:

a. To determine the proportion of patients using QVA149 with a history of the following conditions:
   - Cardiovascular conditions: unstable ischemic heart disease, congestive heart failure, myocardial infarction, cardiac arrhythmia (brady- and tachyarrhythmias), atrial flutter/fibrillation, cerebrovascular conditions (hemorrhagic or ischemic stroke, transient ischemic attack [TIA]) and hypertension
   - Long QT-syndrome or prolonged QT_c interval (>450 ms)
   - Diabetes mellitus
   - Glaucoma (narrow-angle glaucoma and others)
   - Bladder obstruction/urinary retention
   - Chronic renal failure
   - Liver disease
   - Pregnancy or breast-feeding at initiation of QVA149
b. To determine the proportion of new initiators of QVA149 with an uninterrupted use for more than one year
c. To obtain long-term exposure data in patients using QVA149 continuously for more than 18 months

Secondary objectives

To describe the patient characteristics of new initiators of QVA149 in terms of demographics, COPD characteristics (duration, severity, smoking status), QVA149 exposure (indication, dosage, duration of use and switching patterns), and use of concomitant (respiratory) medications.

Study design

Multinational, multi-database cohort study in new users of QVA149

Setting

The study is based on data derived from five European electronic health care databases (from The Netherlands [NL], Italy [IT], United Kingdom [UK], Denmark [DK] and Spain [ES]).

This final report describes the results of 38 months of data accrual (maximum follow up duration: 28 months), namely from 1st November 2013 until 1st January 2017.

Subjects and study size, including dropouts

For this final report, data were retrieved from the Integrated Primary Care Information Project (IPCI; NL) database, the Aarhus University Prescription Database (Aarhus; DK), THIN (UK), HSD (IT) and SIDIAP (Spain). Patients having had at least one year of valid database history and were newly prescribed/dispensed inhaled QVA149 during the data accrual period were included.

Variables and data sources

Patient characteristics were summarized at the time of the index date (= date of the first QVA149 prescription during the study period). These patient characteristics included demographics (age, gender), indication of use, prescribed daily dosage, concomitant use of other respiratory drugs, concomitant use of drugs with anticholinergic properties, underlying comorbidities (i.e., renal impairment, narrow-angle glaucoma, urinary retention or symptomatic bladder outflow obstruction, cardiovascular and cerebrovascular disease, liver disease and diabetes mellitus), lifestyle factors (smoking), and COPD characteristics (COPD duration and COPD severity).

Results

During the study period (1st November 2013 to 1st January 2017), 14,913 patients having a first-time prescription or dispensation of QVA149 were identified. The median age at time of QVA149 initiation was 70 years and QVA149 was prescribed more frequently to men (63.9%) than women. The majority of patients had moderate to severe COPD.

Off-label use for asthma was 5.5% (database range 1.4-7.2%). When considering off-label use based on indication asthma or asthma/COPD without concomitant use of ICS, the proportion of off-label use was 7.1%. Pre-defined thresholds for off-label use, as specified in the RMP, were not exceeded (i.e., >8% in asthma and >15% in asthma/COPD without concomitant ICS use). Five QVA149 initiators were younger than 18 years, all of which from SIDIAP. The pooled overall proportion of off-label use was 14.2 %.

As expected in an elderly COPD population, with respect to cardio and cerebrovascular comorbidities, the proportion of newly prescribed QVA149 patients with a cardiovascular or cerebrovascular history was high in the pooled databases (ischemic heart disease 13.4% of which unstable ischemic heart disease 7.6%, heart failure 8.5%, arterial hypertension 48.3%, cardiac arrhythmia 11.9%, stroke 6% and TIA 3.1%) but the proportion of patients with a history of malignant cardiac arrhythmia (e.g., malignant ventricular arrhythmia and/or long QT-syndrome) was low (<1.0%).

The proportion of patients with severe or end-stage renal disease was low (<2%), however the proportion of patients with mild (CKD stage 2) (47.9% pooled) or moderate (CKD stage 3) (17.7% pooled) renal impairment was large. The prevalence of other comorbidities of interest such as hepatic impairment and narrow-angle glaucoma was low in all databases, apart from a high prevalence of hepatic impairment in HSD (6.3%). The proportion of patients with a medical history of lower urinary retention/bladder outflow obstruction was below 5%.

Information on dosing was only available for IPCI, THIN and HSD. QVA149 was prescribed according to the defined dose as per product label (i.e., once daily) in 99% of all study patients.

There were two patients (one in THIN and one in HSD), identified as being pregnant during QVA149 use. No patient was identified as lactating during QVA149 use or during the pre-defined periods before first-time prescription of QVA149. Ten percent of patients had at least one year of uninterrupted QVA149 use with the highest proportion in Aarhus (18%) and the lowest proportion in HSD (0%) in line with country specific market uptake. The proportion of

patients with 18 months of uninterrupted QVA149 treatment was low namely 3% in the pooled dataset.

Discussion

Results presented in this final study report show that the majority of first-time prescriptions for QVA149 was in line with the product label with regard to dosing, indication of use and age. Proportions of QVA149 patients in subpopulations considered as high-risk treatment conditions or with missing information in the RMP were in line with prevalence estimates for the COPD population in published literature indicating that QVA149 is considered as treatment option in these patients. Two single QVA149 patients were identified for the subpopulation of pregnant and lactating women suggesting that this population is not treated with QVA149.

Marketing Authorization Holder(s)

Novartis Europharm Ltd

Frimley Business Park

Camberley GU16 7SR

United Kingdom

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

[redacted]

[redacted]

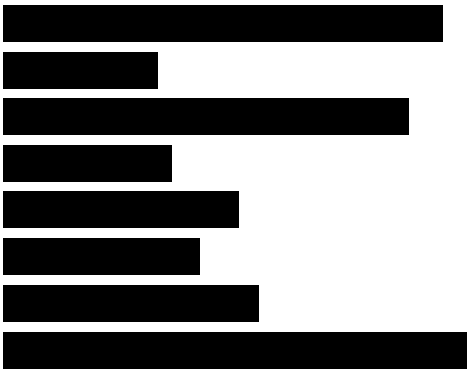
2 List of abbreviations

AB	Antibiotic
ADM	Administrative
AF	Atrial Fibrillation
AFL	Atrial Flutter
(A)MI	(Acute) Myocardial Infarction
AP	Angina Pectoris
ATC	Anatomical Therapeutic Chemical classification system
AV	Atrioventricular
BNF	British National Formulary
BOO	Bladder Outlet Obstruction
BPH	Benign Prostatic Hyperplasia
CAT	COPD Assessment Test
CHMP	Committee for Medicinal Products for human use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CUI	Concept Unique Identifier
CV	Cardiovascular
DK	Denmark
ECG	Electrocardiogram
DUS	Drug Utilization Study
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
EMA	European Medicines Agency
ER	Emergency Room
ES	Spain
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
HSD	Health Search Database
ICD-9	International Classification of Disease, 9th rev.
ICD-10	International Classification of Disease, 10th rev.
ICPC	International Classification of Primary Care
ICS	Inhaled Corticosteroid
IHD	Ischemic Heart Disease

HSD	Health Search Database
IPCI	Integrated Primary Care Information Project
IQ	Interquartile
IT	Italy
LABA	Long Acting β_2-Agonist
LAMA	Long Acting Muscarinic Antagonist
LLN	Lower Limit of Normal
LQTS	Long QT Syndrome
LTRA	Leukotriene Receptor Antagonist
LUTS	Lower Urinary Tract Symptoms
LRTI	Lower Respiratory Tract Infection
MA	Muscarinic antagonist
MR	Medical Record
NEC	Not elsewhere classified
NL	The Netherlands
NOS	Not otherwise specified
OTC	Over-the-counter
PASS	Post Authorization Safety Study
PDE	Phosphodiesterase
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSVT	Paroxysmal Supraventricular Tachycardia
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RRE	Remote Research Environment
SABA	Short Acting β_2-Agonist
SAC	Scientific Advisory Committee
SAMA	Short Acting Muscarinic Antagonist
SD	Standard Deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
SVT	Supraventricular Tachycardia
TIA	Transient Ischemic Attack
TG	Triglycerides
THIN	The Health Improvement Network
UK	United Kingdom
UMLS	Unified Medical Language System
VT	Ventricular Tachycardia
WHO	World Health Organization

3 Investigators

Project lead



Principal investigators (PI)

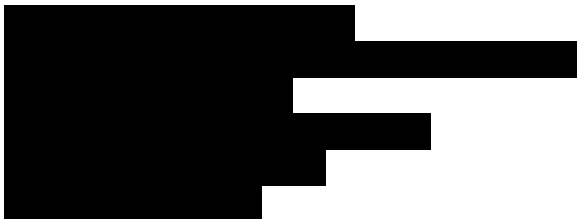
Sub-investigators

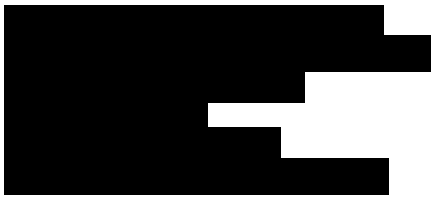
[redacted]

4 Other responsible parties

Marketing authorization holder (contact person)

Scientific advisory committee





5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 November 2013	01 November 2013	None
End of data collection* for interim report 1	Q4 2014	12 December 2014	None
Registration in the EU PAS register	After PRAC/CHMP approval of the protocol	30 October 2014	None
Interim report 1	Q1 2015	16 March 2015	None
End of data collection* for interim report 2	Q1 2016	22 February 2016	None
Interim report 2	Q2 2016	24 May 2016	None
End of data collection* for final report of study results	Q1 2017	9 August 2017	None
Final report of study results	Q4 2017	05 November 2017	None

*Date from which the analytical dataset is completely available (ENCePP 2015)

6 Rationale and background

According to the GOLD (Global Initiative of Lung Disease) guideline, chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. (GOLD 2017) Exacerbations and comorbidities contribute to the overall severity in individual patients. COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment (GOLD 2017). COPD is a frequent disease and in Europe, the COPD prevalence rates range from 4%-10% in the adult population (Halbert et al 2006).

Bronchodilators are the mainstay of symptomatic management of COPD and include β_2-adrenergic agonists, and muscarinic antagonists (MA; also called anticholinergics). Methylxanthines and phosphodiesterase-4 inhibitors reduce both bronchoconstriction and airway inflammation. These drugs are used alone or in combination.

Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered as Seebri® Breezhaler® and related products) indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). QVA149 was approved by the European Commission on 19 September 2013 and was first launched in The Netherlands in November 2013.

Combining a long-acting β_2-adrenergic agonist (LABA) with a long-acting muscarinic antagonist (LAMA) as concurrent therapy has been shown to significantly improve bronchodilation in COPD patients compared to the respective monotherapies (van Noord et al 2010; Wedzicha et al 2016). This is expected to lead to improvement in dyspnea, health status/quality of life and COPD exacerbations compared to monotherapy.

The “missing information” as per the Risk Management Plan (RMP) includes use of QVA149 in patients with unstable, clinically significant cardiovascular conditions and long QT-syndrome, type I & II uncontrolled diabetes, use in patients with severe liver impairment, use in patients with moderate to severe kidney impairment, use in pregnancy and lactation, long-term use in COPD beyond 18 months, use in COPD not related to smoking or smoking exposure less than 10 pack-years, and use in patients with ethnic origin other than Caucasian and Asian as use in these patients was excluded from the RCTs.

In the context of the QVA149 marketing authorization application, the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed MAH’s proposal to conduct a drug utilization study (DUS) to address aspects related to drug utilization, off-label use, and identification of patient groups, which have not yet or insufficiently been studied in the pivotal clinical trials of QVA149 (i.e., so called ‘missing information’ outlined in the RMP).

This report contains the results of the final analysis of this DUS.

7 Research question and objectives

7.1 Primary objectives

1. To determine the proportion of patients using QVA149 who do not meet the criteria specified in the QVA149 label ('off-label use') i.e., use of QVA149 in patients younger than 18 years or in patients without a diagnosis of COPD or in patients with asthma/asthma and COPD without concomitant use of inhaled corticosteroids (ICS)*[1]
2. To determine the proportion of patients using QVA149 who have missing information as per RMP or high risk treatment conditions:
    a. To determine the proportion of patients using QVA149 with a history of the following conditions:
        - Cardiovascular conditions: unstable ischemic heart disease, congestive heart failure, myocardial infarction, cardiac arrhythmia (brady- and tachyarrhythmias), atrial flutter/fibrillation, cerebrovascular conditions (hemorrhagic or ischemic stroke, transient ischemic attack [TIA]) and hypertension
        - Long QT-syndrome or prolonged QT_c interval (>450 ms)
        - Diabetes mellitus
        - Glaucoma (narrow-angle glaucoma and others)
        - Bladder obstruction/urinary retention
        - Chronic renal failure
        - Liver disease
        - Pregnancy or breast-feeding at initiation of QVA149 (if available)
    b. To determine the proportion of new initiators of QVA149 with an uninterrupted use for more than one year
    c. To obtain long-term exposure data in patients using QVA149 continuously for more than 18 months

7.2 Secondary objectives

To describe the patient characteristics of new initiators of QVA149 in terms of:

- Demographics (age and gender)
- Indication (COPD, COPD and asthma [with or without ICS*], asthma [without COPD], other)
- COPD duration (from diagnosis of COPD until first prescription of QVA149)
- COPD disease severity
- COPD exacerbation (need of oral corticosteroids and/or hospitalization for COPD) in 1 year prior to first prescription of QVA149

[1] *Concomitant use of ICS is defined as at least one prescription of ICS within ± 90 days of the first prescription of QVA149.

- Smoking status at time of first prescription of QVA149
- Prescribed dosage/posology
- Duration of QVA149 exposure (in days)
- Switching patterns (switching to and from other treatments)
- Co-prescription with other respiratory drugs
- Concomitant use of other anticholinergic drugs

8 Amendments and updates to the protocol

Table 8-1 Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
1	30-Oct-2014	Table 9-6	Clarification that country estimates reflect population ≥ 40 years of age	Update based on PRAC's recommendation of points for consideration' no. 3
2	30-Oct-2014	9.9 Limitation of research methods	Discussion of the validity of the approach to obtain antibiotic use for treatment of LRTI and specification of category "other/unknown"	Update based on PRAC's recommendation of 'points for consideration' no.1
3	30-Oct-2014	9.9 Limitation of research methods	Discussion of potential misclassification of results for hepatic injury when using diagnosis code of "liver enzymes abnormal."	Update based on PRAC's recommendation of 'points for consideration' no. 2
4	30-Oct-2014	11 Management and reporting of adverse events/reactions	Re-wording according to PRAC's request.	Update based on PRAC's recommendation of 'points for consideration' no. 4
5	30-Oct-2014	9.3.9 Pregnancy or breast-feeding at initiation of QVA149	Pregnancy will be assessed within 274 days (= 9 months) before QVA149 initiation but also during first QVA149 use.	

			Breast feeding will be assessed within 365 days before QVA149 but also during first QVA149 use.	
6	September 2016	9.4.5.Description of Switching from another respiratory drug to QVA149	Conduct a sensitivity analysis extending the switching window to 2 weeks	Upon request by the PRAC
7	September 2016	9.9.4 Sensitivity analysis - Off-label use	Perform a stratified analysis of off-label use (with respect to asthma) in patients younger than 40 and 40 years or older and add duration of asthma	Upon request by the PRAC
8	September 2016	9.9.4 Sensitivity analysis – Off-label use	Conduct a sensitivity analysis excluding missing from denominator	Upon request by the PRAC

9 Research methods

9.1 Study design

This is a multinational, multi-database cohort study using five electronic health care databases from various European countries, namely the Netherlands (NL), Italy (IT), the United Kingdom (UK), Denmark (DK), and Spain (ES) (for details on the databases, see Section 9.5 'Data sources and measurement'). As QVA149 was not launched at the same time in the countries of the participating databases (see Table 9-1), the maximum duration of follow-up varies across databases: 12 months for HSD, 20 months for SIDIAP, 24 months for THIN, 25 months for Aarhus and 28 months for IPCI.

For this final report a cohort of patients newly treated with QVA149 was selected. Patient characteristics were assessed either at time of first QVA149 prescription or during a pre-defined period prior to first prescription.

9.2 Setting

The study is based on data derived from five European electronic health care databases (from the Integrated Primary Care Information [IPCI] Project database (The Netherlands), the Health Search Database [HSD] (Italy), The Health Improvement Network [THIN] database (United Kingdom), Aarhus University Prescription Database [Aarhus] (Denmark), and Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] database) (Spain). This report presents the results of 38 months of data accrual

(maximum follow up duration: 28 months), namely from 1st of November 2013 to 1st January 2017. Based on the different data-updates, for Aarhus, HSD and SIDIAP, data was used from 1st November 2013 until 31st December 2015, for IPCI, data was used from 1st November 2013 until 1st February 2016 and for THIN from 1st November 2013 until 1st January 2017.

For more detailed information on the individual databases, see Section 9.5 'Data sources and measurement'.

The launch dates of QVA149 in the countries of the databases are shown below:

Table 9-1 Launch dates for QVA149 in the five participating countries

Country	Actual launch date
Denmark	25 November 2013
Italy	10 March 2014
Netherlands	01 November 2013
Spain	15 April 2014
United Kingdom	01 Dec 2014

9.3 Subjects

9.3.1 In- and exclusion criteria

From the databases containing available QVA149-exposure data from November 2013 onwards, a cohort of patients with a first-time prescription or dispensation of QVA149 was selected.

Patients without one year of database history before the first prescription of QVA149 were excluded from the study. No further exclusion criteria were applied.

9.3.2 Follow-up

Patients initiating QVA149 were followed from time of the first prescription until the earliest of (i) end of treatment, (ii) end of data collection, (iii) disenrollment from the database or (iv) death. Follow-up was needed to determine duration of use and occurrence of pregnancy/lactation during QVA149 exposure. No safety outcomes were captured during follow-up.

9.4 Variables

9.4.1 QVA149 exposure and duration of use

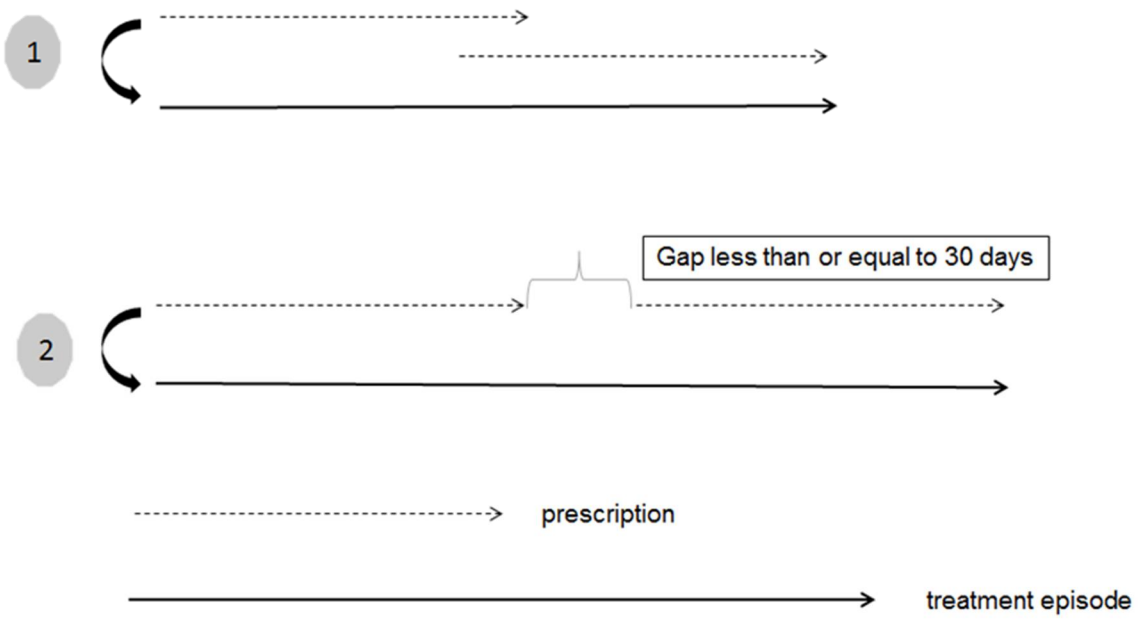
Patients prescribed QVA149 were identified in the databases by an automated search of the respective Anatomical Therapeutic Chemical (ATC) classification system codes, product names and/or Multilex codes from the prescription records (see Annex 2.3 – Exposure definition – respiratory medication use).

Episodes of drug exposure were created from prescription data. For each drug prescription the end date of the prescription was calculated based on the amount of drug prescribed and the actual dosing regimen of the individual patient. If dosing information was missing, the total

amount (per prescription) was divided by the recommended dose according to the SmPC of the respective drug (i.e., glycopyrronium 50 µg / indacaterol 110 µg for QVA149 or other respiratory drugs/drug classes of interest [for the assessment of concomitant use of other respiratory drugs]). This duration of use was then added to the start date of the prescription, which yielded a stop date for each prescription.

From the individual prescriptions, episodes of use were created taking into account potential overlap and gaps (Figure 9-1). If a subsequent prescription overlapped a previous prescription, the two prescriptions were combined into one episode and the stop-date of that episode was the stop-date of the latest prescription (see (1) in Figure 9-1). In case of a gap between two prescriptions, these prescriptions were only combined into one episode if the duration of the gap was less than or equal to 30 days (see (2) in Figure 9-1). The treatment episode ended at either (i) the stop date of the last prescription or (ii) the end of data collection for the final analysis or (iii) time of disenrollment from the database or (iv) date of death, whichever came first.

Figure 9-1 Creation of treatment episodes for QVA149



Patient characteristics are summarized as per the start of the first treatment episode (= index date).

9.4.2 Demography, life style factors and COPD characteristics prior to time of first prescription

The following information was retrieved from the databases (where available):

- For all patients, information on gender and age (at time of first prescription of QVA149) was captured
- If available, information on smoking status was retrieved; patients were classified as "current smoker", "past smoker", "never-smoker" or "smoking status unknown" at the time of first prescription.
- Duration of COPD (from date of first-recorded diagnosis of COPD until date of first prescription)
- Number of COPD exacerbations requiring hospitalization (including emergency room [ER] visits for reasons of COPD exacerbation) or need of oral corticosteroids in the year prior to the index date. Hospitalization was determined either via linkage with hospital admission/discharge database (Aarhus) and SIDIAP, or using a combination of COPD codes (see Annex 2.4 – COPD definition, Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of QVA149+codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics) with information from hospital referral and discharge letters (IPCI and HSD) or using a combination of disease codes with source codes (hospital discharge letters) (THIN)
- COPD severity at time of first prescription of QVA149 (see Annex 2.4 – COPD definition). COPD severity was assessed by spirometry, if available. If spirometry data were lacking or the date of spirometry was more than 5 years prior to the index date, COPD severity was categorised according to published algorithms.
- Number of courses of antibiotics (AB) for treatment of lower respiratory tract infections or COPD exacerbations in the year prior to the index date. If the indication of use was missing in the prescription file, a search was conducted for disease diagnosis codes of pneumonia, acute bronchitis or COPD exacerbation at the time (in the period 1 month before and 1 week after AB prescription date) of prescription of the antibiotic. (see Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of QVA149+codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics)

9.4.3 Indication of use of inhaled QVA149

For each patient initiating treatment with QVA149 the indication of use was assessed. Indication of use was classified as follows:

- COPD
- COPD and asthma (with and without concomitant ICS use)
- Asthma (without COPD)
- Other (neither COPD nor asthma recorded in database)
- Missing

The indication of use was identified in the database based on disease-specific codes (see Annex 2.4 – COPD definition, Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of QVA149+codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics).

The indication of use was retrieved either directly from the drug prescription or drug dispensing records. If missing, the indication of use was retrieved from the patient's medical

file ("journal") where disease codes for COPD and/or asthma were queried. For COPD as indication of QVA149-use, we considered the complete medical record of the patient. However, asthma as indication of QVA149-use was only considered if the recorded date of asthma fell within a maximum period of 1 year prior to the index date. If QVA149 was prescribed for reasons other than COPD or asthma, the respective respiratory disease codes were provided. If information on the indication of use was missing, indication of use was labeled as "missing".

9.4.4 Prescribed dosage/posology

Each capsule contains 110 µg of indacaterol and 50 µg of glycopyrronium equivalent to a delivered dose of 85 µg of indacaterol and 43 µg of glycopyrronium. The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro® Breezhaler® inhaler or related products.

Although the recommended dose of QVA149 is the inhalation of the content of one capsule once daily, in this study the frequency of use was assessed as follows, based on the patient-specific dosing regimen (if available):

1. Once daily
2. Every other day
3. Twice daily
4. Other (all other dosing regimens)

For those databases not containing records of dosing regimen, assessment of the prescribed dosage was not possible (i.e. Aarhus and SIDIAP).

9.4.5 Switching patterns (switching to and from other treatments)

Switching patterns of QVA149 were also evaluated. Patients could either switch to another drug, or start a prescription with another drug as add-on therapy.

Switching involved the following:

1. Switching from QVA149 to single use LABA (or vice versa)
2. Switching from QVA149 to single use LAMA (or vice versa)
3. Switching from QVA149 to combination of LABA and LAMA (either fixed or loose) (or vice versa)
4. Switching from QVA149 to combination of LABA+ICS (either fixed or loose) (or vice versa)
5. Switching from QVA149 to loose combination of LAMA+ICS (or vice versa)
6. Switching from QVA149 to combination of LABA, LAMA and ICS (LABA+ICS either fixed or loose) (or vice versa)

Add-on therapy was defined as a prescription of the other drug (or combination of drugs) starting at the same day as the QVA149 prescription. Thus to define add-on therapy, the prescription date of QVA149 was similar to the prescription date of the other respiratory drug.

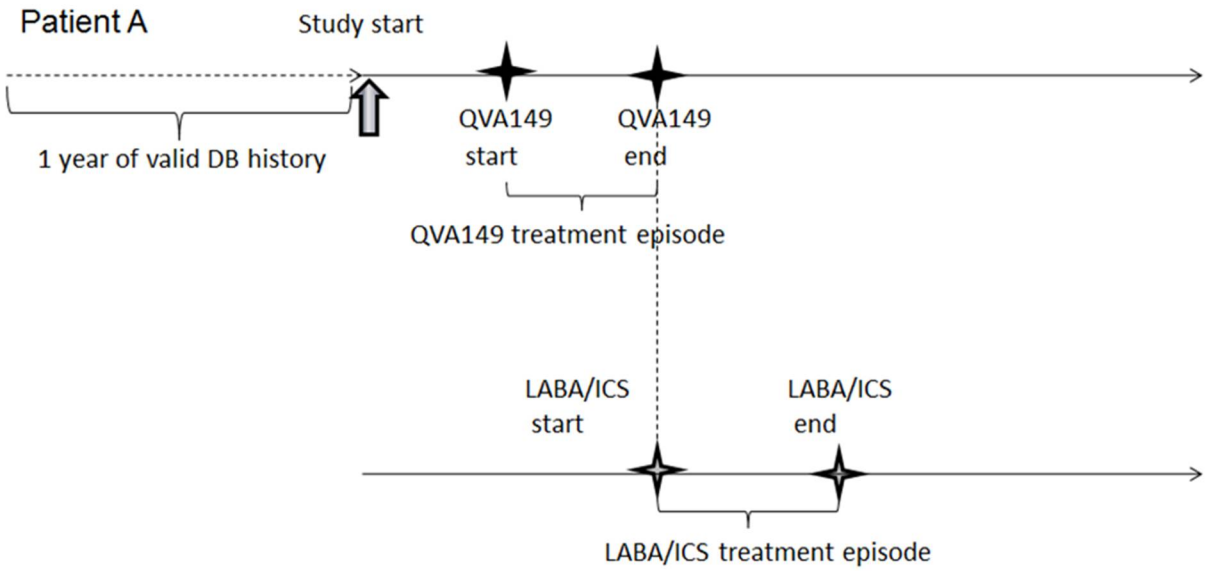
Switching from QVA149 to another respiratory drug was defined as an ongoing or started prescription of the other drug (or combination of drugs) on the day following the end date of

the QVA149 prescription period. This characteristic could only be defined for patients for whom the complete duration of the QVA149 prescription fell within the follow-up of the patient.

In the example as described in Figure 9-2, a patient prescribed QVA149 was considered as having switched therapy as prescriptions of QVA149 were no longer continued and treatment of LABA/ICS was initiated.

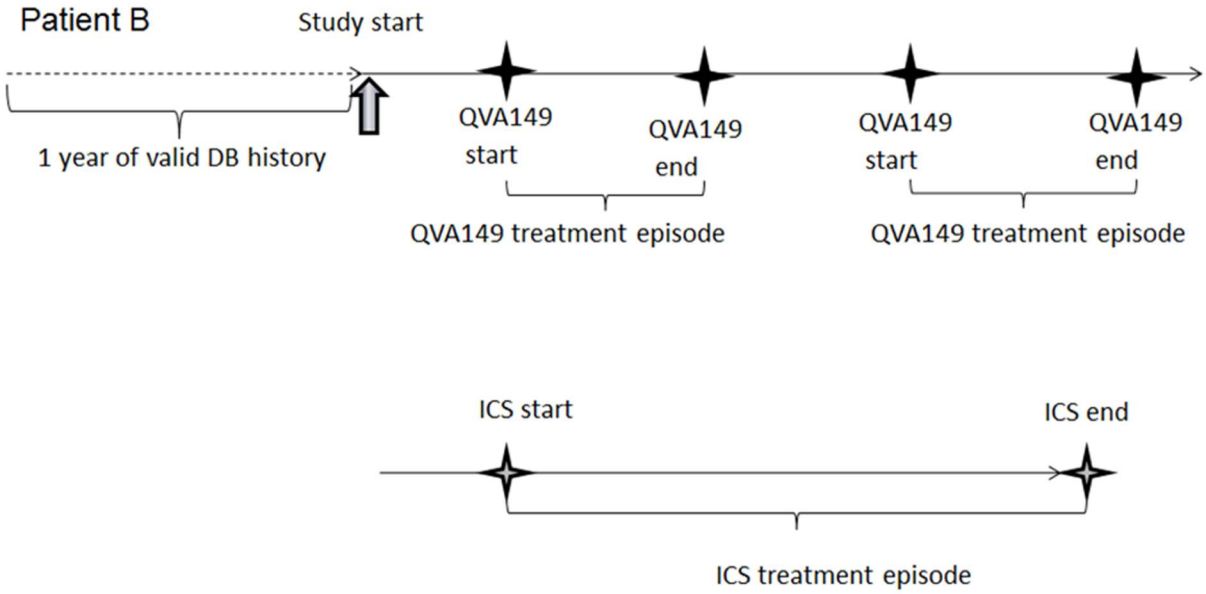
Switching from another respiratory drug to QVA149 was defined as an ongoing prescription of the other drug (or combination of drugs) on the day before start of the QVA149 prescription. within the analysis, the proportion of QVA149 patients previously on LABA, LAMA, loose or fixed combination of LABA and LAMA, LABA+ICS (fixed or loose), LAMA+ICS or LABA+LAMA+ICS (fixed or loose) at the time of first prescription of QVA149 were summarized, as well as the proportions with one of these drugs as add-on next to QVA149. Similarly, the proportion of patients on the non-QVA149 therapies that switched to QVA149 was also summarized.

Figure 9-2 QVA149 switching



Add-on therapy was defined when another respiratory drug was initiated on the same day of the QVA149 prescription.

Figure 9-3 QVA149 add-on therapy



9.4.6 Concomitant use of other respiratory drugs

Information on concomitant use of QVA149 with other respiratory drugs was retrieved from the prescription records and was assessed in the six months prior to the index date (including drugs initiated at index date). These drugs were retrieved via an automated search for either ATC or Multilex codes (see Annex 2.3 – Exposure definition – respiratory medication use). The following types of bronchodilating and anti-inflammatory drugs/drug classes were considered as respiratory drugs:

- Short-acting muscarinic antagonists (SAMAs)
- Single-ingredient inhaled long-acting muscarinic antagonist(LAMAs)
- Single-ingredient short-acting β2-adrenergic agonists (SABAs)
- Single-ingredient inhaled long-acting β2-adrenergic agonists (LABAs)
- Inhaled corticosteroids (ICS)
- Xanthines
- Fixed combination therapy (LABA + inhaled corticosteroids, SAMA + SABA, SABA+other respiratory drugs, LABA+LAMA)
- Oral β2-agonists
- Leukotriene receptor antagonists (LTRAs)
- Systemic corticosteroids
- Oral phosphodiesterase- 4 (PDE-4) inhibitors

9.4.7 Concomitant use of systemic anticholinergic drugs

Information on the concomitant use of other systemic anticholinergic drugs was retrieved from the prescription records and was assessed in the six months prior to the index date

(including drugs initiated at index date). These drugs were retrieved via an automated search for either ATC or Multilex codes (see Annex 2.6 – Concomitant medication use). The following types of drugs were considered as anticholinergic drugs:

- Antipsychotic drugs
- Tricyclic and tetracyclic antidepressant agents
- Disopyramide
- Antispasmodics
- Antiparkinsonian agents
- Cholinesterase inhibitors
- Atropine
- H1-antihistamines
- Anticholinergics for treatment of overactive bladder in patients with bladder outlet obstruction

9.4.8 Underlying comorbidities

Underlying comorbidities were assessed during the complete database history prior to and including the index date. Underlying comorbidity was identified via an automated search for disease-specific codes (see Annex 2.2 - Comorbidity definition).

Comorbidities of interest were the following:

- Chronic kidney disease (with relevant stages)
- Diabetes mellitus
- Narrow-angle glaucoma
- Urinary retention or symptomatic bladder outflow obstruction
- Benign prostatic hyperplasia (BPH)
- Cardiovascular disease including
  - unstable ischemic heart disease (= unstable angina pectoris and myocardial infarction)
  - heart failure
  - myocardial infarction
  - cardiac arrhythmia= atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”/long QT syndrome), atrioventricular (AV) block, supraventricular tachycardia, sick sinus syndrome and premature depolarization. Numbers were provided as separate counts but also combined for severe cardiac arrhythmia (=atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”/long QT syndrome),
  - arterial hypertension
- Cerebrovascular disease (hemorrhagic or ischemic stroke, transient ischemic attack [TIA])
- Hepatic impairment (i.e., hepatic failure, hepatic impairment, liver cirrhosis, hepatitis, increase in liver enzymes)

Renal impairment was identified either via disease specific codes (all databases) for chronic kidney disease (CKD) or via the estimated glomerular filtration rate (eGFR) if serum creatinine levels were available (all databases) (Levey and Coresh 2012).

9.4.9 Pregnancy or breast-feeding at initiation of QVA149

Information on pregnancy or breast-feeding at initiation of QVA149 was available in IPCI, HSD, THIN and SIDIAP where it is captured using specific codes or free text. Codes for pregnancy and/or breast-feeding are described under Annex 2.2 - Comorbidity definition. In Aarhus, information on pregnancy was available via linkage with the Danish birth register.

Pregnancy was assessed within 274 days (= 9 months) before QVA149 initiation but also during first QVA149 use. Breast-feeding was assessed within 365 days before QVA149 but also during first QVA149 use. Whether pregnancy or breast-feeding occurred prior to or during QVA149-use was reported separately.

9.5 Data sources and measurement

For this study, databases containing routine healthcare data were used to provide a reflection of real-world circumstances and prescribing behavior. The databases were selected based on their geographic location, the availability of population-based data on drugs, and their merits and recognized reputation for use in drug utilization and safety research. Multiple countries were included to provide international data and to guarantee sufficient exposure to QVA149. The participating databases are part of the EU-ADR Alliance, a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronic health care record databases is required (EC 2012).

The databases chosen for this study comply with European Union (EU) guidelines on the use of medical data for medical research. (EC 2012)

The databases being used for this study are THIN (United Kingdom [UK]), HSD (Italy [IT]), IPCI (The Netherlands [NL]), the Aarhus University Prescription Database (Denmark [DK]), and SIDIAP (Spain [ES]). Table 9-2 provides an overview of the data sources. These databases have a mean follow-up ranging from 3.3 to 15.0 years. The databases are representative of the country-specific populations in terms of age and gender. These databases are primary care databases (except for the Aarhus database from Denmark, which is a prescription database linked to all other Danish registries) and the available patient records are considered to be complete, as they originate from the general practitioner's (GP's) electronic primary care records who acts as gatekeeper on the patient's medical care. The primary care databases represent 3%-13% of the respective country-specific total population. As of 2016, the total number of active persons in the source population encompassing all five databases is around 14 million.

Table 9-2 Overview of databases

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
Country	Netherlands	United Kingdom	Denmark	Italy	Spain
Type of database	MR	MR	ADM	MR	MR
Number of patients,	2,2	3.8	1.4	1.1	5.6

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
millions					
Mean follow-up in the database (years)	3.2	7.3	15.0	11.5	7.7
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	Yes	No	No
Updates	Once a year (June)	Three times per year (January/May/September)	Yearly (April)	Twice per year (June/December)	Yearly (April/May)
Prescriptions					
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Inpatient Rx	missing	missing	missing	missing	missing
Coding of drugs	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	No
Outcomes					
Hospitalizations	Yes (might be incomplete as no linkage with hospital database)	Yes (might be incomplete as no linkage with hospital database)	Yes	Yes (might be incomplete as no linkage with hospital database)	Yes
Inpatient diagnoses	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes	Yes (might be incomplete if missing discharge letter or if diagnosis not recorded by GP)	Yes
Outpatient diagnoses	Yes	Yes	Yes	Yes	Yes
Coding of diseases	ICPC	READ	ICD-10	ICD-9 CM	ICD-10

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; ICD= International Classification of Disease, ICPC = International Classification of Primary Care; MR = Medical Records; Rx = Prescription

More detailed information on the databases is presented in Annex 2.7 – Data sources.

9.6 Bias

There is the potential for diagnostic bias, as comorbidity was assessed via disease-specific codes. If disease coding is inconsistent or differential, this could result in diagnostic bias. Previous validation studies have shown that coding is reliable in these databases and that they are suitable for pharmacoepidemiologic research (Vlug et al 1999; Lewis et al 2007; Ehrenstein et al 2010; Cazzola et al 2011; Garcia-Gil Mdel et al 2011) however these studies, except for the study by Cazzola, did not focus on respiratory research and underlying comorbidity. For this study, indication of use of QVA149 in relation to off-label use is one of the study objectives. However, the recording of the indication of use might be incomplete or

missing, as is the case for Aarhus. If missing, the indication of use was retrieved from the patient's medical file ("journal") where disease codes for COPD and/or asthma were queried. For COPD as indication of QVA149-use, we considered the complete medical record of the patient. However, asthma as indication of QVA149-use was only considered if the recorded date of asthma fell within a maximum period of 1 year prior to the index date. In addition, as data is used from electronic primary care databases and a prescriptions database (with linkage to the hospital and out-patient registry) (Aarhus), information on important covariates such as spirometry and smoking status might be missing or reported inconsistently. In general, missing information relating to disease codes, indication of use, pulmonary function and smoking status could introduce bias if non-recording of these data is was carried out systematically (i.e., non-randomly). Further sources of bias and their potential effects on study results are discussed in Section 10.2 – Limitations.

9.7 Study size

This DUS is an exploratory, descriptive study. The study size consists of the sum of new initiators of QVA149 derived from each database. As no hypothesis is being tested and prediction of market uptake of a new product is difficult, it was decided to include a minimum of 3,000 patients initiating QVA149 (including all databases) within three years of product launch.

9.7.1 Statistical procedure characteristics for off-label use

Off-label use is monitored utilizing a conjugate Bayesian binomial-beta model.

The following thresholds are considered in the study:

1. The probability for off-label use in asthma and mixed asthma/COPD without ICS co-medication to exceed the proportion of 15% should be below 90%
2. The probability for off-label use in a pure asthmatic population to exceed the proportion of 8% should also be below 90%

Exceeding the thresholds of 90% in either case constitutes a trigger for risk minimization activities. Concomitant use of ICS was defined as at least one prescription of ICS within ± 90 days of the index date.

For the test, the prior was based on the historical data from German IMS-Disease Analyzer (DA) database for the free combination of LAMA & LABA (N=30,711; asthma only- 7.0% (n=2,145); Asthma only & COPD with Asthma not on ICS – 10.3% (n=3,163): Source: IMS-DA database, Germany; data on file). Allowing for a contribution of these historical data of 10% of the sample size, inclusion of 3,000 patients into the study yields the following characteristics for the statistical procedure using decision rule for detecting of off-label use (Table 9-3):

Table 9-3 Statistical procedure characteristics

Off-label population	Null hypothesis percentage	Alternative hypothesis percentage	Type 1 error	Power
Asthma	8%	10%	6%	99%
Asthma/COPD with asthma without ICS	15%	17%	2%	82%

This power of 99% and 82% respectively indicates that the proposed sample size of 3,000 is sufficient to describe off-label use of QVA149 in this study.

9.7.2 Estimation of two-sided confidence intervals for comorbidities

Two-sided confidence intervals (CIs) for background prevalence of comorbidities listed in the table below were estimated using the exact (Clopper-Pearson) method. This estimation was based upon the proposed overall sample size of 3,000.

Table 9-4 Estimated two-sided, ninety-five percent confidence intervals per comorbidity (N=3,000)

Comorbidity	Background prevalence (%)*	Estimated 95% CI
Cerebrovascular disease	4.2	3.51 - 4.98
Myocardial Infarction	4.8	4.06 - 5.63
Chronic liver disease	5.0	4.25 - 5.84
Glaucoma	5.3	4.53 - 6.16
Chronic renal failure	6.3	5.46 - 7.23
Heart Failure	7.2	6.30 - 8.18
Cardiac arrhythmia	7.2	6.30 - 8.18
Ischemic heart disease	8.4	7.43 - 9.45
Diabetes mellitus	12.2	11.05 - 13.42
Atrial fibrillation	13.0	11.82 - 14.26
QTc prolongation	13.4	12.20 – 14.67
Hypertension	27.4	25.81 – 29.03

Source: *We used conservative estimates of background prevalence from: (Suruki et al 2009; Feary et al 2010; Schneider et al 2010; Cazzola et al 2012; Divo et al 2012; Garcia-Olmos et al 2013)

Based upon this estimation, a sample size of 3,000 produces a two-sided 95% CI of 3.51 - 4.98 when the background percentage is 4.2. Similarly, a sample size of 3,000 produces a two-sided 95% CI of 25.81 - 29.03 when the background percentage is 27.4% (see Table 9-4 for details). Therefore, Novartis believes that the proposed sample size of 3,000 is sufficient to describe the use of QVA149 in patients with different cardiovascular or other comorbidities (including missing information).

9.8 Data transformation

This final report describes data from five different databases (THIN, IPCI, Aarhus, HSD and SIDIAP). Data were extracted, validated and cleaned locally. All databases use different coding schemes (e.g. ICD9-CM (HSD) and ICD-10 (Aarhus, SIDIAP), ICPC (IPCI), READ

(THIN)) and their content comes from different data sources (e.g., GP records, hospital discharge diagnoses, and death registries). To reconcile the differences across terminologies, a shared semantic foundation was built for the definition of events under study by selecting disease concepts from the Unified Medical Language System (UMLS, V.2008AA). The sequential steps of this process are described below:

1. Identification of Unified Medical Language System® (UMLS®) concepts

A UMLS concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event/comorbidity, a medical definition was created and, based on such definition; relevant UMLS concepts were identified and projected into the database-specific terminologies.

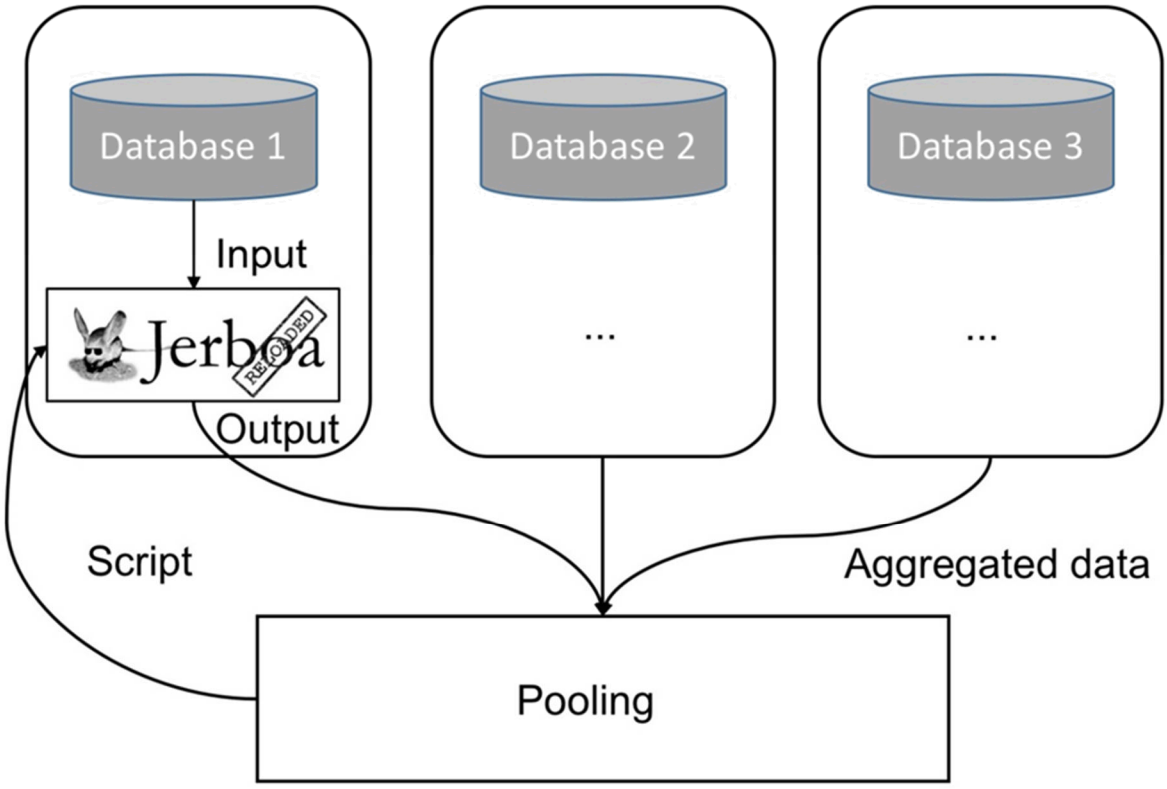
2. Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm was constructed for each comorbidity based on the consensus of the data providers. This data extraction algorithm was then implemented by all databases.

3. Event data extraction

Subsequently, each database extracted data using a common data model, i.e. standardized patient, drug, and event files linkable via a patient unique identifier. These files were managed locally by purpose-built software called Jerboa, which transformed the input files in de-identified aggregated output; files (see Figure 9-4). These output files were transmitted to a central secured environment (remote research environment) for pooling and further processing. Jerboa has been developed for the EU-ADR FP7-ICT project (www.EU-ADR-project.org) that combines health care data of 30 million individuals in Europe to detect adverse drug events. It has been used in many other EU funded projects (i.e., SOS: www.sos-nsaids-project.org; VAESCO: www.vaesco.net) and EMA tender protocols.

Figure 9-4 Model for data sharing and elaboration



Source: www.EU-ADR-project.org

4. Benchmarking of disease prevalence rates

For each comorbidity of interest, database-specific prevalence rates using Jerboa were benchmarked. The observed prevalence rates were compared with the prevalence rates of the other databases and with prevalence rates estimated from previous database studies and literature. Outliers were identified and further investigated in an iterative manner.

9.9 Statistical methods

9.9.1 Main summary measures

For this final report, the following data are described:

- Number of patients in the QVA149 exposure cohorts
- Indication of use and dosing of QVA149
- Duration of QVA149 use, proportion of patients with an uninterrupted use for more than one year and more than 18 months
- Baseline characteristics in terms of demography, life style factors and COPD characteristics at or prior to first QVA149 prescription

- Baseline characteristics in terms of comorbidity and concomitant drug use at or prior to first QVA149 prescription

Categorical variables were summarized using contingency tables. Continuous variables were summarized using the mean and standard deviation (SD) or median with P25, P75 and minimum and maximum values.

Off-label use is presented separately for off-label use due to age and off-label indication. The proportion of patients with a potential off-label indication was calculated as the number of patients with an indication asthma, COPD and asthma without concomitant use of ICS divided by the overall number of QVA149 initiators for whom information on indication of use was available.

For the calculation of off-label use for indication other than COPD or asthma and for the total off-label use, missing values (=category = unknown) were included in the denominator. Upon request by the PRAC, a sensitivity analysis was conducted excluding the missings for the calculation of total off-label use and use for indication other than COPD or asthma.

The percentage of patients with indication asthma and the percentage with indication asthma or with indication COPD plus asthma without concomitant use of ICS were analyzed with a conjugate Bayesian beta-binomial model. As prior information, historical data from the German IMS-Disease Analyzer (DA) database was used, where the percentage with an indication of "Asthma only" was 7.0% and the percentage with an indication of "Asthma only" (regardless of ICS use) or with an indication "COPD with asthma" and no concomitant ICS use was 10.3%. In the present study, the prior for the Bayesian analysis was constructed with contribution of these historical data for 10% of the sample size of the new study.

For the group "Asthma only" the probability of exceeding the proportion of 8% is reported. For the combined group "Asthma only" plus "COPD with asthma without ICS", the probability of exceeding the proportion of 15% is reported.

Upon request by the Scientific Advisory Committee (SAC) and PRAC, the analysis of off-label use for asthma and off-label use for indication asthma or indication COPD plus asthma without concomitant use of ICS was repeated stratifying by age category (<40 years and >= 40 years).

9.9.2 Main statistical methods

Categorical data are presented as counts (n) and proportions (%) with 95% CIs. Although for determining the sample size, Clopper-Pearson CIs were used, Wilson's (score) method was used for the 95% CIs in the reports, as this gives appropriate coverage probabilities (Agresti and Coull 1998). For continuous data, the number of observations (n), mean, SD, and median (with minimum and maximum values) are presented.

For this final report, data are presented by country and pooled over all databases. Additionally, an analysis by calendar year was performed to evaluate trends over time.

9.9.3 Missing values

No imputation of missing values was done. Missings were represented in a separate category. In- or exclusion of the number of missing values in the denominator was applied depending

on the relevance for each characteristic. Missing values were removed from the denominator for the calculation of smoking status and COPD severity. With respect to calculation of off-label use, missing values were not included in the denominator for the off-label use in "asthma" and "COPD & Asthma without ICS". For the calculation of off-label use for indication other than COPD or asthma and for the total off-label use, missing values (category = unknown) were included in the denominator. Upon request by the PRAC, a sensitivity analysis was conducted excluding the missings for the calculation of total off-label use and use for indication other than COPD or asthma.

9.9.4 Sensitivity analyses

For the calculation of off-label use for indication other than COPD or asthma and for the total off-label use, missing values (=category = unknown) were included in the denominator. Upon request by the PRAC, a sensitivity analysis was conducted excluding the missings for the calculation of total off-label use and use for indication other than COPD or asthma.

9.9.5 Amendments to the statistical analysis plan

Based on SAC and/or PRAC recommendations made during review of previous interim study reports, the percentages of off-label use because of indication asthma was also stratified by age group (<40 yrs, ≥40 yrs). Furthermore, the duration of asthma was provided. Asthma duration is the time between first recorded asthma event and initiation of QVA149.

9.10 Quality control

The study is conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (ISPE 2008) and according to the ENCePP code of conduct (EMA 2013).

All programs were programmed according to agreed coding standards and were validated by double programming or source code review with second programmer involvement.

Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) was used for statistical analysis.

10 Results

For this final report of the QVA149 DUS, data from five participating databases were used (i.e., IPCI, THIN, Aarhus, HSD and SIDIAP).

10.1 Participants

The individual study period for the respective databases is described in Table 10-1. These study periods are based on the most recent data releases of the respective databases. The overall study period was from 1st November 2013 until 1st January 2017.

In total, more than 14 million eligible patients were identified during the study period. Eligible patients are considered as patients with at least one year of medical history and still present in the database during the study period. The number of eligible patients per database is also described in Table 10-1.

Table 10-1 Number of eligible patients during study period

	THIN [UK]*	IPCI [NL]	Aarhus [DK]**	HSD [IT]***	SIDIAP [ES]
Study period	1st Nov 2013 - 1st Jan 2017	1st Nov 2013 – 1st Feb 2016	1st Nov 2013 – 31st Dec 2015	1st Nov 2013 – 31st Dec 2015	1st Nov 2013 – 31st Dec 2015
Number of eligible patients during study period	3,323,247	1,886,883	1,437,787	1,238,432	6,145,459

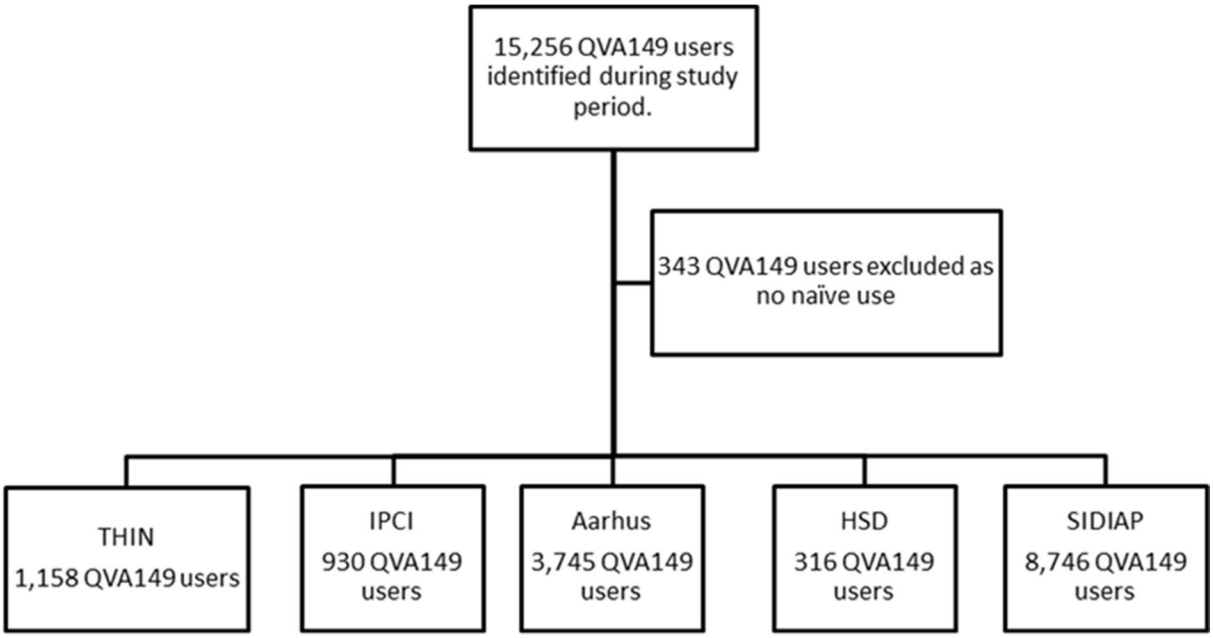
* = based on the THIN mid-year count in 2016; **=based on subset of patients in the database for whom lung function data are available (i.e., FEV1) and optimal linkage to hospital & out-patient registers exist ; ***=based on active patients in the database (of note: previous interim reports presented eligible patient numbers for HSD that were not limited to active patients only)

10.2 Descriptive data

10.2.1 Baseline characteristics of QVA149 users

In total, 15,256 QVA149 initiators were identified, of which 343 were excluded for not having one year of valid database history before their first QVA149-prescription. (see Figure 10-1).

Figure 10-1 Patient selection flowchart



In total, 14,913 incident users of QVA149 remained in the study cohort: 316 in HSD, 930 in IPCI, 1,158 in THIN, 3,745 in Aarhus and 8,764 in SIDIAP. Baseline characteristics of QVA149 initiators are shown in Table 10-4.

Based on pooled data, the median age at time of QVA149 initiation was 70 years, and 202 patients (1.0%) were under 40 years of age at the time of first QVA149 prescription of whom five were below the age of 18 (0.1%) (see also Section 10.4.1 Off-label use of QVA149).

A total of 5,739 patients (38.5%) had at least one year of follow-up after QVA149-initiation and the proportion of patients with 18 months of follow-up was lower namely 12.9%.

Overall, QVA149 was prescribed more frequently to men (63.9%) than women. The proportion of men varied between databases and was highest in SIDIAP (71.9 [95% CI 70.9 - 72.8%]) and lowest in THIN (49.6 [95% CI: 46.7-52.4%]).

Among patients for whom information on smoking status was available (87.0% of the pooled study population), approximately one third of QVA149 initiators were current smokers, 41.0% were never-smokers, and 28.8% were past-smokers. The high proportion of patients "never smokers" was driven by the SIDIAP database (58.6 % "never smokers"). The proportion of current smokers ranged from 23.6-46.0% and the proportion of past-smokers ranged from 17.9-52.9%. Largest differences between databases were observed for never-smokers with proportions of 17.8% and 58.6% for HSD and SIDIAP, respectively, and a much lower range for the other databases (6.5-8.4%) (see appendices Figure 15-1 Smoking status).

Baseline characteristics of the database-pooled study population by calendar year are presented in the appendices (see appendices Table 15-1 Baseline characteristics of the QVA149 cohort – by calendar year). The majority of QVA149 initiators (98.7%) 'entered' the study in 2014 and 2015. Differences in gender distribution and smoking status were observed for 2016 versus 2014 and 2015. These differences can be explained by differences in database and not necessarily differences over time as 2016 data mainly represent THIN data. The number of patients in 2013 and 2017 is too low to draw conclusions on differences over calendar time.

Table 10-2 Baseline characteristics of the QVA149 cohort (N=14,913) by database and pooled

Characteristic	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Gender												
Female	584 (50.43)	47.56- 53.31	379 (40.75)	37.64- 43.94	1,857 (49.59)	47.99- 51.19	103 (32.59)	27.66- 37.95	2,466 (28.14)	27.21- 29.09	5,389 (36.14)	35.37- 36.91
Male	574 (49.57)	46.69- 52.44	551 (59.25)	56.06- 62.36	1,888 (50.41)	48.81- 52.01	213 (67.41)	62.05- 72.34	6,298 (71.86)	70.91- 72.79	9,524 (63.86)	63.09- 64.63
Age												
Mean (SD)	69.53 (10.90)		67.71 (10.26)		70.55 (10.23)		72.58 (9.44)		70.23 (12.10)		70.15 (11.43)	
Median (IQ range)	70.62 (62.64-77.24)		67.82 (60.61-75.12)		71.08 (64.35-78.00)		73.56 (67.10-78.75)		71.17 (63.25-79.17)		70.96 (63.35-78.50)	
Min-max	26.10-97.84		39.64-96.63		20.68-100.94		38.89-104.85		15.08-100.83		15.08-104.85	
Age category												
<18	0 (0)	0-0.33	0 (0)	0-0.41	0 (0)	0-0.1	0 (0)	0-1.2	5 (0.06)	0.02- 0.13	5 (0.03)	0.01- 0.08
18 < 40	7 (0.60)	0.29- 1.24	1 (0.11)	0.02- 0.61	17 (0.45)	0.28- 0.73	1 (0.32)	0.06- 1.77	171 (1.95)	1.68- 2.26	197 (1.32)	1.15- 1.52
40 < 60	213 (18.39)	16.27- 20.73	216 (23.23)	20.63- 26.05	548 (14.63)	13.54- 15.80	29 (9.18)	6.47- 12.87	1,405 (16.03)	15.28- 16.81	2,411 (16.17)	15.58- 16.77
60 – 80	746 (64.42)	61.62- 67.13	599 (64.41)	61.28- 67.42	2,474 (66.06)	64.53- 67.56	221 (69.94)	64.67- 74.73	5,208 (59.42)	58.39- 60.45	9,248 (62.01)	61.23- 62.79
> 80	192 (16.58)	14.55- 18.83	114 (12.26)	10.30- 14.52	706 (18.85)	17.63- 20.14	65 (20.57)	16.48- 25.37	1,975 (22.54)	21.67- 23.42	3,052 (20.47)	19.83- 21.12
Smoking status (assessed at index date)*												
Missing	0 (0.00)	0.00-0.33	69 (7.42)	5.90- 9.28	1565 (41.79)	40.22- 43.38	47 (14.87)	11.37- 19.22	316 (3.61)	3.24- 4.02	1,997 (13.39)	12.85- 13.95

Characteristic	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Current smoker	452 (39.03)	36.26-41.87	396 (45.99)	42.69-49.33	955 (43.81)	41.74-45.90	101 (37.55)	31.97-43.47	1,994 (23.60)	22.71-24.52	3,898 (30.18)	29.39-30.98
Past smoker	612 (52.85)	49.97-55.71	393 (45.64)	42.34-48.98	1,083 (49.68)	47.58-51.78	120 (44.61)	38.79-50.58	1,508 (17.85)	17.05-18.68	3,716 (28.77)	28.00-29.56
Never-smoker	94 (8.12)	6.68- 9.83	72 (8.36)	6.69-10.40	142 (6.51)	5.55- 7.63	48 (17.84)	13.73-22.86	4,946 (58.55)	57.49-59.59	5,302 (41.05)	40.20-41.90
Follow-up time (assessed at index date)												
Mean (SD)	0.74 (0.51)		0.92 (0.59)		1 (0.58)		0.33 (0.22)		0.86 (0.44)		0.88 (0.50)	
Median (IQ range)	0.65 (0.28-1.13)		0.87 (0.42-1.38)		0.99 (0.53-1.52)		0.29 (0.16-0.5)		0.84 (0.5-1.16)		0.84 (0.49-1.25)	
Min-max	0-1.97		0-2.3		0-2.1		0-1.04		0.01-1.67		0-2.3	
Number of patents with 1 year follow-up or more	355 (30.66)	28.07-33.37	407 (43.76)	40.61-46.97	1,868 (49.88)	48.28-51.48	4 (1.27)	0.49-3.21	3,105 (35.43)	34.43-36.44	5,739 (38.48)	37.71-39.27
Number of patients with 18 months of follow-up or more	121 (10.45)	8.82-12.34	188 (20.22)	17.76-22.92	974 (26.01)	24.63-27.44	0 (0)	0-1.2	636 (7.26)	6.73-7.82	1919 (12.87)	12.34-13.41

*Percentage of patients for whom smoking status is known; CI=confidence interval; SD=standard deviation

10.2.2 COPD characteristics of patients initiating QVA149

COPD characteristics, which were assessed during the year prior to initiation of QVA149, are described in detail in Table 15-2 COPD characteristics. To assess COPD severity, the most recent spirometry data (where available) up to a maximum of five years prior to QVA149-initiation were used.

The pooled median duration of COPD was 4.7 years with the shortest median duration for Aarhus (3.8 years) and the longest median duration for SIDIAP (5.0 years). The number of patients identified with COPD exacerbations requiring hospitalization was 8% with the lowest proportion in HSD (0.0%) and the highest proportion in THIN (12.7%). The pooled proportion of use of systemic corticosteroids for treatment of COPD exacerbation in the year prior to index date was 9.1%, however, large variations were observed across databases with a proportion of only 4.6% for SIDIAP and 25.5% for IPCI. The proportion of patients using antibiotics for treatment of lower respiratory tract infection (LRTI) or COPD exacerbation in the year prior to index date ranged from 13.0% (HSD) to 33.7% (IPCI), with a pooled estimate of 18.1%.

Spirometry to assess COPD and/or COPD severity was available for THIN (64.3% of study patients), IPCI (44.1%), Aarhus (12.3%), HSD (33.5%), SIDIAP (53.6%) (pooled 43.0%). The number of patients assessed as not having COPD based on spirometry data was high (27.9% in pooled dataset) with the highest proportion for HSD (42.5%). Only spirometry data up to five years prior to QVA149 initiation was considered for the assessment. Based on the pooled data, 6.8% of patients had mild COPD, 49.1% moderate, 37.7% severe and 6.4% very severe. Comparing severity stages across databases, the proportion of patients with mild COPD was higher in IPCI and THIN than in the other databases. The proportion of severe (45.3%) and very severe COPD (17.3%) was the highest for Aarhus (see Figure 15-2 COPD severity by spirometry).

When assessing COPD severity in all patients with information on FEV_1 percentage of predicted, irrespective whether the patient had COPD according to GOLD, the proportion of patients with mild COPD (in the pooled dataset) increased from 6.8% to 13.6%. The other COPD severity categories remained constant.

If spirometry was missing, COPD severity was assessed by proxy (i.e., according to published algorithms). When assessed by proxy, the majority of patients was found to have moderate (60.3% pooled) COPD and 10.1% had severe COPD (see Figure 15-3 COPD severity by proxy).

10.2.3 Prescribed dosage and treatment duration of QVA149

For those databases with information on dosing (THIN, IPCI and HSD), the prescribed dosage of QVA149 was “once daily” for > 99% of patients (Appendices - Table 15-3).

The pooled median duration of use of QVA149 was 88 days and ranged between 60 days (HSD and SIDIAP) and 115 days (Aarhus) (Appendices - Table 15-3).

10.2.4 Switching patterns (switching to and from other treatments)

Switching patterns are presented in Annex 2.1 - Results tables and figures. In the pooled dataset, the proportion of patients not using any other respiratory drug as maintenance therapy on the day before QVA149 initiation was 64.2%. This proportion was the lowest for THIN (39.6%) and the highest for SIDIAP (74.8%). In THIN, patients mainly switched from previous use of LAMA (22.5%), in IPCI and Aarhus, patients mainly switched from previous use of LAMA (12.2 and 10.3% respectively) and previous use of LABA/LAMA/ICS (12.0 and 10.9% respectively) and in HSD and SIDIAP, patients mainly switched from LABA/ICS (12.7 and 7.3% respectively). The proportion of patients switching from previous use of LAMA/ICS to QVA149 was low in all databases (0.5-1.8%) (see Table 15-5 Switching from other respiratory drugs to QVA149). In a sensitivity analysis, the window to determine previous use, was extended from one day to two weeks. In this analysis, the proportion of patients not using any other respiratory drug as maintenance therapy in this period of two weeks before QVA149 initiation decreased to 54.4% but the same pattern with regard to previous use of respiratory drugs remained (Table 15-7 Switching from other respiratory drugs to QVA149 (assessed in 14 days prior to the index date).

Add-on therapy defined as use of QVA149 combined with prescriptions of LABA, LAMA, LABA/LAMA, LABA/ICS, LAMA/ICS or LABA/LAMA/ICS, on the same date as QVA149, was 15.4% in the pooled dataset with the lowest proportions for THIN (6.9%) and HSD (7.0%) and the highest proportions in SIDIAP (20.2%). QVA149 was mainly combined with LABA/ICS (pooled 6.4% - 8.5% SIDIAP). The high add-on therapy in SIDIAP could represent misclassification because in SIDIAP only the month and year of drug dispensing is available, with the prescription date always set to the first day of the prescription month (see Table 15-9 Add-on therapy (assessed on index date)).

When studying switching from QVA149 to another drug, the proportion of patients that could not be assessed because of short duration of follow-up was high in THIN, IPCI, Aarhus and HSD (47.3, 35.4, 40.5 and 53.8% respectively). For those patients with adequate follow-up, the proportion of patients no longer on treatment with respiratory drugs, assessed on the day following QVA149 discontinuation, was 82.1% in the pooled dataset (range 66.9-87.8%). When treatment with QVA149 was discontinued, patients mainly switched to LABA/ICS in IPCI (10.0%), Aarhus (9.0%), HSD (6.2%) and SIDIAP (5.5%). In THIN, patients mainly switched to LABA/LAMA/ICS (12.1%). Switching to the latter was also high in IPCI (7.3%) and Aarhus (8.5%) (see Table 15-11 Switching from QVA149 to other respiratory drugs).

10.2.5 Comorbidity in patients initiating QVA149

Comorbidity was assessed at index date and in the complete medical history of patients initiating QVA149 prior to index date. Findings of this analysis are presented in detail in Table 15-16 History of comorbidities in patients initiating QVA149.

The comorbidities defined as primary study objectives are described in Section 10.4.2.

10.2.6 Use of other drugs in patients initiating QVA149

10.2.6.1 Respiratory drugs

Use of other respiratory drugs on or in the six months prior to index date is presented in detail in Table 15-18. Use of short-acting bronchodilating medications, especially SABA, was high with a pooled proportion of 43.9 % for SABA. Obvious differences were observed between databases. The use of short-acting β2-agonists was especially high in THIN (87.6%) and the lowest in HSD (14.2%). Use of other short-acting agents such as SAMA (pooled 15.8%) or the combination of SAMA+SABA (pooled 1.8%) was much lower than SABA, and country-specific differences were observed (i.e., use of SAMA was almost non-existent in Denmark, whereas the combination of SAMA+SABA was very low in the UK (0.2%) and Spain (0.5%).

In the pooled dataset, 22.7% of patients initiating QVA149 had been prescribed an ICS in the six months prior to index date with the highest proportions for Spain (26.0%) and Italy (28.5%).

With respect to the use of long-acting bronchodilating medications (LABA or LAMA) the proportion of patients using LAMA (pooled 45.8%) was higher than LABA (pooled 26.8%) with the largest differences in THIN. The fixed combination of LABA+ICS was frequently prescribed (database-pooled proportion 30.8%) with database specific proportions ranging between 30.5-37.7%). Previous use of the fixed combination of LABA+LAMA was low in all databases except for THIN where the proportion was 3.4%.

In the pooled dataset, 29.2% of patients received a systemic corticosteroid in the 6 months prior to index date, with the highest proportions in THIN (38.3%). When considering use of systemic corticosteroids indicated for “COPD exacerbation” only, the pooled proportion was 7.3% (19.8% in IPCI, 13.4% in THIN, 11.2 % in Aarhus, 3.8% in HSD and 3.7% in SIDIAP).

Large differences in the use of xanthines in the six months prior to index date were observed, with the highest proportion observed for Italy (7.3%) and lowest proportion for Aarhus (0.6%%) (database-pooled proportion 1.9%). Proportion of LTRA-use in the pooled dataset was 2.7%. Use of other respiratory medications such as oral β2-agonists and PDE-4 inhibitors was low (<2%) in all databases.

10.2.6.2 Drugs with anticholinergic effects

Amongst products with anticholinergic effects, mainly antidepressants (tricyclic and tetracyclic), antipsychotic agents and H1-antihistaminics were prescribed (see Table 15-20). Use of other product classes with anticholinergic effects, such as anticholinergics for overactive bladder (except for THIN), antispasmodics, disopyramide, antiparkinson drugs, cholinesterase inhibitors and atropine was low (<5%).

10.3 Outcome data

Not applicable.

10.4 Main results

10.4.1 Off-label use of QVA149

Table 10-3 presents off-label use in terms of indication and age, by database and pooled.

Off-label use due to age

In SIDIAP, there were five patients younger than 18 years at the time of first QVA149 prescription, all of which were female. The age at QVA149 initiation ranged between 15-17.5 years. Four of these patients took QVA149 for one month and one patient took QVA149 for a consecutive period of 2 months. With regard to the indication of use, one patient used QVA149 for asthma, in two patients the indication of use was not specified, one patient had "wheezing" as indication of use and in one patient, the only respiratory code at time of QVA149 prescribing was "nasopharyringitis". Spirometry data was only available in one patient and FEV1/FVC was > 70%. None of these patients had underlying comorbidity.

Off-label indication of use in patients initiating QVA149

For Aarhus, information on the indication of use was only available based on disease codes retrieved from ambulatory care or hospital admission. For the other databases, indication of use was either retrieved from the prescription files or from information on disease codes as registered in the patients file. Table 15-13 presents indication of use of QVA149 if different from COPD or asthma.

In the pooled dataset, the proportion of patients using QVA149 for asthma only was 5.5% with the lowest proportion for HSD (1.4%), 1.9% for Aarhus, 2.3% for THIN, 3.8% for IPCI and 7.2% for SIDIAP. The proportion of patients using QVA149 for asthma or asthma and COPD without concomitant use of ICS (defined as no prescription of ICS (fixed or loose) within ± 90 days of the index date) was 7.1% in the pooled dataset with database specific proportions of 1.8% for HSD, 2.5% for Aarhus, 6.6% for IPCI, 7.2% for THIN and 8.6% for SIDIAP.

These percentages resulted in probabilities of <0.1% to exceed the 8% (asthma indication) and 15% (asthma/COPD) thresholds defined in the RMP, i.e., both probabilities were below 90%.

Upon request by the SAC, the analysis of off-label use was repeated in patients younger than 40 years and patients 40 years or older. The analysis of off-label use was hindered in the young patients because of low numbers. Thus only results for SIDIAP and for the pooled dataset are presented. In patients younger than 40 years, the proportion of patients with asthma was expected to be higher than in patients older than 40 years. This is reflected by a higher proportion of QVA149 off-label use because of asthma (48.6%) and a higher proportion of patients using QVA149 for asthma or asthma/COPD without concomitant use of ICS (52.6%). (Table 15-14) In patients 40 years or older, these pooled proportions were 4.9% and 6.5% respectively.

The SAC also requested information on median duration of asthma in case patients initiated QVA149 therapy for indication of asthma only (= off-label use). In patients, initiating QVA149 for asthma only, the pooled median duration of asthma was 8.6 years in patients younger than 40 years and 6.9 years in patients 40 years or older.

Overall proportion of off-label use

The pooled overall proportion of off-label use was 14.2% (95% CI 13.7-14.8) with the lowest proportion in Aarhus (2.7%; 95% CI 2.2-3.3) and HSD (2.5%, 95% CI 1.3-4.9). The proportions were higher in THIN (12.0%, 95% CI 10.3-14.0), IPCI (9.6%, 95% CI 7.8-11.6) and SIDIAP (20.4%, 95% CI 19.6-21.3). When patients with missing values were excluded from the denominator, the overall proportion of off-label use increased to 16.6% (95% CI 15.9-17.2) (pooled dataset). (Table 15-13)

Table 10-3 QVA149 – off-label use (by database and pooled)

		THIN [UK] (N=1,158)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,745)			HSD [IT] (N=316)			SIDIAP [ES] (N=8,764)			Pooled Data (N=14,913)		
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
Off-label because of indication asthma[#]																			
	Yes	26 (2.31)	1.58-3.36	<0.0001	35 (3.78)	2.73-5.21	<0.0001	44 (1.89)	1.41-2.52	<0.0001	3 (1.36)	0.46-3.91	<0.0001	595 (7.24)	6.70-7.83	0.00260	703 (5.48)	5.1-5.89	<0.0001
	No	1,100 (97.69)	96.64-98.42		892 (96.22)	94.79-97.27		2,288 (98.11)	97.48-98.59		218 (98.64)	96.09-99.54		7,627 (92.86)	92.29-93.40		12125 (94.52)	94.11-94.9	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.95		1413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2085 (13.98)	13.43-14.55	
Off-label because of indication asthma or indication COPD & asthma without ICS[#]																			
				P> 15%			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**
	Yes	81 (7.19)	5.83-8.85	<0.0001	61 (6.58)	5.16-8.36	<0.0001	58 (2.49)	1.93-3.20	<0.0001	4 (1.81)	0.71-4.56	<0.0001	705 (8.58)	8.00-9.21	<0.0001	909 (7.09)	6.65-7.54	<0.0001
	No	1,045 (92.81)	91.15-94.17		866 (93.42)	91.64-94.84		2,274 (97.55)	96.85-98.11		217 (98.19)	95.44-99.29		7,517 (91.53)	90.90-92.11		11,919 (92.91)	92.46-93.35	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.95		1,413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2,085 (13.98)	13.43-14.55	
Off-label because of indication 'other'	Yes	58 (5.01)	3.89-6.42		28 (3.01)	2.09-4.32		43 (1.15)	0.85-1.54		4 (1.27)	0.49-3.21		1,080 (13.15)	12.44-13.90		1,213 (8.13)	7.71-8.58	
	No	1,068 (92.23)	90.54-93.63		899 (96.67)	95.31-97.64		2,289 (61.12)	59.55-62.67		217 (68.67)	63.36-73.53		7142 (86.96)	86.21-87.67		11,615 (77.89)	77.21-78.54	

		THIN [UK] (N=1,158)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,745)			HSD [IT] (N=316)			SIDIAP [ES] (N=8,764)			Pooled Data (N=14,913)		
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.94		1,413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2,085 (13.98)	13.43-14.55	
Off-label because of age																			
	Yes	0 (0)	0-0.33		0 (0)	0-0.41		0 (0)	0-0.1		0 (0)	0-1.2		5 (0.06)	0.02-0.13		5 (0.03)	0.01-0.08	
	No	1,158 (100.0)	99.67-100.0		930 (100.00)	99.59-100.00		3,745 (100.00)	99.90-100.00		316 (100.00)	98.80-100.00		8,759 (99.94)	99.87-99.98		14908 (99.97)	99.92-99.99	
Off-label total																			
	Yes	139 (12.00)	10.26-14.00		89 (9.57)	7.84-11.63		101 (2.70)	2.22-3.27		8 (2.53)	1.29-4.92		1,787 (20.39)	19.56-21.25		2,124 (14.24)	13.69-14.81	
	No	987 (85.23)	83.07-87.16		838 (90.11)	88.02-91.86		2,231 (59.57)	57.99-61.13		213 (67.41)	62.05-72.34		6,437 (73.45)	72.51-74.36		10,706 (71.79)	71.06-72.51	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.94		1,413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		540 (6.16)	5.68-6.68		2,083 (13.97)	13.42-14.53	

missing excluded from denominator for calculation of off-label use, CI=Confidence interval

10.4.2 Cardiovascular and cerebrovascular comorbidities

Approximately 1 patient in 2 was diagnosed with arterial hypertension (pooled 48.3%) with the lowest proportion in Aarhus (29.8%) and the highest proportion in HSD (58.5%). (Table 10-4)

In the pooled dataset, the proportion of patients with a history of ischemic heart disease was 13.4% with the highest proportion in Aarhus (22.0%) and the lowest proportion in HSD (7.9%). Among patients with ischemic heart disease, in the pooled dataset, the proportion was the highest for angina pectoris (AP) (9.2%) followed by MI (6.6%) and unstable AP (1.8%).

The proportion of heart failure in the pooled dataset was 8.5% and ranged from 7.6-10.5% across databases.

A history of cardiac arrhythmia (= a medical history of atrial flutter/fibrillation, AV-block, ventricular tachycardia/fibrillation or Long QTc/Torsade de Pointes) was reported in 11.9% (ranging from 10.8-14.9%). The proportion of patients with malignant ventricular arrhythmia was 0.5% or lower.

The proportion of patients with a history of stroke was 6.0% in the pooled dataset and ranged from 5.4 to 8.9% per database. The proportion of TIA was 3.1% in the pooled dataset and ranged from 2.5-6.7% across databases.

Database-specific results for cardiovascular and cerebrovascular comorbidities are depicted in Figure 15-5 and presented in detail in the Appendices (see Table 15-16 and Table 15-17). The prevalences of the respective comorbidities of interest over calendar time mainly represent the characteristics of the respective databases with SIDIAP predominance in 2014 and 2015 and THIN predominance in 2016. The number of patients in 2013 and 2017 are too low to make calendar year specific assumptions.

Table 10-4 Cardiovascular and cerebrovascular comorbidities (selected items)

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Cerebrovascular events:												
Stroke	77 (6.65)	5.35- 8.23	83 (8.92)	7.26-10.93	230 (6.14)	5.42- 6.96	28 (8.86)	6.20-12.51	469 (5.35)	4.90- 5.84	887 (5.95)	5.58- 6.34
TIA	57 (4.92)	3.82- 6.32	62 (6.67)	5.24- 8.45	106 (2.83)	2.35- 3.41	14 (4.43)	2.66- 7.30	221 (2.52)	2.21- 2.87	460 (3.08)	2.82- 3.37
Cardiovascular events:												
Ischemic heart disease:	230 (19.86)	17.67- 22.26	197 (21.18)	18.68-23.92	823 (21.98)	20.68- 23.33	25 (7.91)	5.42-11.42	724 (8.26)	7.70- 8.86	1,999 (13.40)	12.87- 13.96
Myocardial infarction	95 (8.20)	6.76- 9.93	103 (11.08)	9.22-13.25	292 (7.80)	6.98- 8.70	15 (4.75)	2.90- 7.68	474 (5.41)	4.95- 5.90	979 (6.56)	6.18- 6.97
Angina pectoris	206 (17.79)	15.69- 20.10	113 (12.15)	10.20-14.41	735 (19.63)	18.39- 20.93	11 (3.48)	1.95- 6.12	307 (3.50)	3.14- 3.91	1,372 (9.20)	8.75- 9.67
Unstable angina pectoris	32 (2.76)	1.96- 3.88	23 (2.47)	1.65- 3.68	147 (3.93)	3.35- 4.60	1 (0.32)	0.06- 1.77	69 (0.79)	0.62- 1.00	272 (1.82)	1.62- 2.05
Unstable ischemic heart disease (unstable AP and/or MI combined)	113 (9.76)	8.18-11.60	119 (12.80)	10.80-15.10	366 (9.77)	8.86-10.77	16 (5.06)	3.14- 8.07	526 (6.00)	5.52- 6.52	1,140 (7.64)	7.23- 8.08
Heart failure	121 (10.45)	8.82-12.34	93 (10.00)	8.23-12.10	352 (9.40)	8.51-10.38	27 (8.54)	5.94-12.15	668 (7.62)	7.08- 8.20	1,261 (8.46)	8.02- 8.91
Arterial hypertension	540 (46.63)	43.77- 49.51	390 (41.94)	38.80-45.13	1116 (29.80)	28.36- 31.28	185 (58.54)	53.04- 63.84	4972 (56.73)	55.69- 57.77	7,203 (48.30)	47.5-49.1
Cardiac arrhythmia:												
Atrial fibrillation/flutter	125 (10.79)	9.14-12.71	103 (11.08)	9.22-13.25	548 (14.63)	13.54- 15.80	36 (11.39)	8.34-15.37	926 (10.57)	9.94-11.23	1,738 (11.65)	11.15- 12.18
Ventricular tachycardia	0 (0.00)	0.00- 0.33	5 (0.54)	0.23- 1.25	16 (0.43)	0.26- 0.69	1 (0.32)	0.06- 1.77	15 (0.17)	0.10- 0.28	37 (0.25)	0.18- 0.34

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Ventricular fibrillation	0 (0.00)	0.00- 0.33	5 (0.54)	0.23- 1.25	3 (0.08)	0.03- 0.24	0 (0.00)	0.00- 1.20	12 (0.14)	0.08- 0.24	20 (0.13)	0.09- 0.21
TDP/Long QT syndrome	0 (0.00)	0.00- 0.33	2 (0.22)	0.06- 0.78	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	2 (0.01)	0.00- 0.05
Severe cardiac arrhythmia combined	125 (10.79)	9.14-12.71	110 (11.83)	9.91-14.06	556 (14.85)	13.74- 16.02	37 (11.71)	8.62-15.72	944 (10.77)	10.14- 11.44	1772 (11.88)	11.37- 12.41

TIA=Transient ischemic attack; TDP=Torsades de Pointes; AP=Angina pectoris; Myocardial infarction; CI=confidence interval

10.4.3 Missing information in the RMP and high-risk treatment conditions

Chronic kidney disease (CKD) was assessed either via disease code or based on eGFR. The proportion of patients with CKD stage 2 (a creatinine clearance between 60-89 mL/min/1.73m^2) was high and ranged between 42.1-50.5% (pooled 47.9%). The proportion of patients with CKD – stage 3 (eGFR 30-59 mL/min/1.73m^2) ranged between 13.8-31.8% (pooled 17.7%). (Table 10-5)

The pooled prevalence of urinary retention was 1.8% and ranged between 1.0-3.2% across databases. The prevalence of BPH was high in HSD (21.2%) and SIDIAP (21.1%) and lower in the other databases (range 5.1-7.5%).

The pooled prevalence of diabetes mellitus was 19.9%, with the lowest proportion in Aarhus (9.5%) and ranged between 18.3-24.6% in the other databases.

The number of patients with narrow-angle glaucoma was small (<0.5%) in all databases as well as in the pooled population; the pooled prevalence of non-narrow-angle glaucoma was 5.6%. The pooled proportion of patients with hepatic impairment was 1.5%, with differences between databases (range 0.9 (SIDIAP) – 6.3% (HSD)).

There were two women identified as being pregnant during QVA149 treatment, one in THIN (UK) and one in HSD (IT). The database records of these patients were reviewed and there was no information on a negative outcome of these pregnancies (no codes for abortion) but further information on these pregnancies was not found in the medical records. No women were identified as lactating during QVA149 treatment. There were no records of pregnancy during the pre-specified periods (<=274 days) before QVA149 initiation.

Database-specific results for missing information in the RMP and high risk treatment conditions by database and calendar year are described in the appendices (Table 15-16 and Table 15-17).

Table 10-5 Underlying conditions corresponding to populations defined in the "Missing information section" of the RMP or who have high risk treatment conditions

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Conditions	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Urinary retention or symptomatic bladder outflow obstruction	37 (3.20)	2.33- 4.37	12 (1.29)	0.74- 2.24	58 (1.55)	1.20- 2.00	3 (0.95)	0.32- 2.75	152 (1.73)	1.48- 2.03	262 (1.76)	1.56- 1.98
BPH#	59 (5.09)	3.97- 6.52	70 (7.53)	6.00- 9.40	238 (6.36)	5.62- 7.18	67 (21.20)	17.06- 26.04	1853 (21.14)	20.30- 22.01	2,287 (15.34)	14.77- 15.92
Diabetes mellitus	212 (18.31)	16.19-20.64	178 (19.14)	16.74-21.79	354 (9.45)	8.56- 10.43	67 (21.20)	17.06- 26.04	2155 (24.59)	23.70- 25.50	2,966 (19.89)	19.26- 20.54
Narrow-angle glaucoma	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	17 (0.45)	0.28- 0.73	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	17 (0.11)	0.07- 0.18
Other glaucoma	47 (4.06)	3.07- 5.36	33 (3.55)	2.54- 4.94	67 (1.79)	1.41- 2.27	26 (8.23)	5.68- 11.78	667 (7.61)	7.07- 8.18	840 (5.63)	5.27- 6.01
Stage 1 (kidney damage with eGFR>= 90 mL/min/1.73m2)**	1 (0.09)	0.02- 0.49	0 (0.00)	0.00- 0.41	0 (0.00)	0.00- 0.10	29 (9.18)	6.47- 12.87	0 (0.00)	0.00- 0.04	30 (0.20)	0.14- 0.29
Stage 2 (eGFR 60-89 mL/min/1.73m2)	574 (49.57)	46.69-52.44	440 (47.31)	44.12-50.53	1862 (49.72)	48.12- 51.32	133 (42.09)	36.77- 47.60	4135 (47.18)	46.14- 48.23	7,144 (47.90)	47.10- 48.71
Stage 3 (eGFR 30-59 mL/min/1.73m2)	368 (31.78)	29.16-34.52	128 (13.76)	11.70-16.13	654 (17.46)	16.28- 18.71	82 (25.95)	21.43- 31.05	1402 (16.00)	15.24- 16.78	2,634 (17.66)	17.06- 18.28
Stage 4 (eGFR 15-29 mL/min/1.73m2)	39 (3.37)	2.47- 4.57	11 (1.18)	0.66- 2.11	70 (1.87)	1.48- 2.35	18 (5.70)	3.63- 8.82	117 (1.34)	1.12- 1.60	255 (1.71)	1.51- 1.93
Stage 5 (eGFR< 15 or dialysis)	4 (0.35)	0.13- 0.88	2 (0.22)	0.06- 0.78	4 (0.11)	0.04- 0.27	10 (3.16)	1.73- 5.73	19 (0.22)	0.14- 0.34	39 (0.26)	0.19- 0.36

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Conditions	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Stage unknown	7 (0.60)	0.29- 1.24	15 (1.61)	0.98- 2.64	25 (0.67)	0.45- 0.98	0 (0.00)	0.00- 1.20	160 (1.83)	1.57- 2.13	207 (1.39)	1.21- 1.59
No CKD disease*	165 (14.25)	12.35-16.38	334 (35.91)	32.89-39.05	1130 (30.17)	28.72- 31.66	44 (13.92)	10.54- 18.18	2931 (33.44)	32.46- 34.44	4,604 (30.87)	30.14- 31.62
Liver disease	65 (5.61)	4.43- 7.09	26 (2.80)	1.91- 4.06	40 (1.07)	0.79- 1.45	20 (6.33)	4.13- 9.57	75 (0.86)	0.68- 1.07	226 (1.52)	1.33- 1.72
Pregnancy or breast-feeding												
-Pregnancy in the 274 days prior to QVA149 initiation	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	0 (0.00)	0.00- 0.03
-Pregnancy during QVA149 use	1 (0.09)	0.02- 0.49	0 (0.00)	0.00- 0.41	0 (0.00)	0.00- 0.10	1 (0.32)	0.06- 1.77	0 (0.00)	0.00- 0.04	2 (0.01)	0.00- 0.05
-Breast feeding in the 365 days prior to QVA149 initiation	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	0 (0.00)	0.00- 0.03
-Breast feeding during QVA149 use	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	0 (0.00)	0.00- 0.03

BPH= Benign Prostatic Hyperplasia, CKD=Chronic kidney disease; CKD=Chronic kidney disease; **CKD stage based on both disease codes and lab results. If CKD stage based on both disease codes and lab results were available, CKD stage closest and most severe to the index date was reported; *Stage 1 based on disease codes for CKD stage 1 only; *Defined as no event of CKD available AND no serum creatinine measurement OR this measurement results in a GFR ≥90 mL/min/1.73m^2 #BPH=Benign prostatic hyperplasia, CI=confidence interval

10.4.4 Uninterrupted use of QVA149 for more than one year

In the pooled dataset, 10% of patients had at least one year of uninterrupted QVA149 use with the highest proportion in Aarhus (18%) and the lowest proportion in HSD (0.0%) in line with country-specific market uptake.). Among patients with at least 1 year of follow-up, the proportion of patients with uninterrupted use was 26%. The number of patients with 18 months of uninterrupted QVA149 treatment was 466 in the pooled dataset which corresponds to 3% of all QVA149 patients and 24% of QVA149 patients with at least 18 months of follow-up. (Appendices - Table 15-3)

The low number of patients with uninterrupted use for more than one year can be explained by the fact that the number of patients with long follow-up upon QVA149 initiation was limited. Indeed, only 38.5% had at least 1 year of follow-up and only 12.9% of patients had at least 18 months of follow-up. (Table 10-2) Especially for patients who were only recently included in the study (i.e. 2015 or later), follow-up was low.

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

According to the guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for reporting of adverse drug reactions from secondary use of data (such as electronic health care databases). The databases used for this study do not include adverse event reports. Information on diseases are captured as diagnosed and coded by physicians in routine medical practice without any relationship to prior drug exposure. This study was designed for the purpose of understanding the drug utilization of QVA149 and no safety outcomes were assessed during follow-up.

11 Discussion

11.1 Key results

During the study period (1st November 2013 to 1st January 2017), 14,913 patients having a first-time prescription or dispensation of QVA149 with one year of valid database history were identified.

With respect to primary objective 1, off-label use for asthma was 5.5% (pooled dataset) and off-label use in patients with asthma or patients with asthma/COPD without concomitant use of ICS was 7.1%. Pre-defined thresholds for off-label use, as specified in the RMP, were not exceeded (i.e., >8% for asthma indication and >15% for asthma/COPD without concomitant ICS use). The proportions of off-label use increased in patients younger than 40 years but numbers were low. There were five patients who were younger than 18 years when initiating QVA149, all within SIDIAP (ES). The pooled overall proportion of off-label use was 14.2 %

Primary objective 2 was to determine the proportion of patients using QVA149 who have missing information as per RMP or high risk treatment conditions. With respect to cardio and cerebrovascular comorbidities, the proportion of newly prescribed QVA149 patients with a

cardiovascular or cerebrovascular history was high in the pooled databases (ischemic heart disease 13.4%, heart failure 8.5%, arterial hypertension 48.3%, cardiac arrhythmia 11.9%, stroke 6% and TIA 3.1%) but the proportion of patients with a history of malignant cardiac arrhythmia (e.g., malignant ventricular arrhythmia and/or long QT-syndrome) was low (<1.0%).

The proportion of patients with severe or end-stage renal disease was low (<2%), however the proportion of patients with mild (CKD stage 2) (47.9% pooled) or moderate (CKD stage 3)(17.7% pooled) renal impairment was large. The prevalence of other comorbidities of interest such as hepatic impairment and narrow-angle glaucoma was low in all databases, apart from a high prevalence of hepatic impairment in HSD (6.3%). The proportion of patients with a medical history of lower urinary retention/bladder outflow obstruction was below 5%.

Information on dosing was only available for IPCI, THIN and HSD. QVA149 was prescribed according to the defined dose as per product label (i.e., once daily) in 99% of all treatment episodes.

There were two patients (one in THIN and one in HSD), identified as being pregnant during QVA149 use. No patient was identified as lactating during QVA149 use or during the pre-defined periods before first-time prescription of QVA149.

Ten percent of patients had at least one year of uninterrupted QVA149 use with the highest proportion in Aarhus (18%) and the lowest proportion in HSD (0.0%) in line with country specific market uptake. The proportion of patients with 18 months of uninterrupted QVA149 treatment was 3.1% in the pooled dataset and the proportion of patients with a follow-up of at least 18 months was 12.9%. Thus, of the patients with at least 18 months of follow-up, almost 1 fourth had uninterrupted QVA149 use.

With respect to the secondary objective, key results for characteristics of QVA149 users are the following: The majority of patients had moderate to severe COPD. Severity assessed by proxy resulted in a small proportion of patients with very severe COPD, as oxygen prescription/use is not routinely recorded in all databases.

11.2 Limitations

The most important limitations of this study relate to the availability and level of detail of the data. Not all potential covariates (i.e., smoking, spirometry data, serum creatinine and proteinuria, indication of use and dosing information) are recorded in all databases and the optimal level of information is not available for all variables. In particular, information on the dose and duration of a prescription is not captured in Aarhus and SIDIAP, hence necessitating estimation based on number of prescribed/dispensed doses, which might lead to misclassification of exposure. In addition, exposure data for SIDIAP is based on prescription and dispensing data. For chronic therapy, patients visit the GP for the first prescription; follow-up medication is dispensed by the pharmacy without need of further prescriptions “electronic dispensation”. The exact date (day/month/year) of pharmacy dispensing is unknown in SIDIAP, dates are available as month/year only. This has the potential to introduce non-differential misclassification of switching as add-on therapy, which explains why the proportion of add-on therapy is higher for SIDIAP compared to the other databases, as all prescriptions in a specific month are set on the first date of that month.

The indication of use is not available in all databases used in this study. Only IPCI captures the indication of use within the prescription files, however, the files are not 100% complete. As the indication of use was one criterion for "off-label" use, the indication of use of QVA149 was assessed by searching the databases for relevant disease codes (COPD or asthma). The validity of this approach depends on the correctness and accuracy of recorded diagnostic coding. Therefore, it is possible that COPD as an indication for prescription of QVA149 is underestimated due to missing COPD codes or coding of respiratory symptoms instead of COPD-specific diagnostic codes. Indeed, when searching for disease codes at or during the period prior to index date, for those cases where asthma or COPD codes were not found, the majority of the codes were for respiratory symptoms or lower respiratory tract infections. Although great effort was made to clarify the indication of use of QVA149, it is difficult to retrieve this information from automated databases especially if based on disease codes only.

COPD severity was assessed by spirometry if available and by proxy if information on spirometry was lacking. Of those patients with spirometry data, 28% (pooled dataset) of patients had an FEV1/FVC of more than 70% and thus were classified as not having COPD. This is correct according to GOLD (which uses the fixed cut-off of 70% for FEV1/FVC) (GOLD 2017). However, in comparison with the Lower Limit of Normal (LLN), this GOLD definition of "obstruction" underestimates the prevalence of COPD in younger patients (but overestimates the prevalence of COPD in older subjects), since the FEV_1/FVC ratio is age-dependent (i.e., ratio decreases with age). The high number of patients diagnosed as not having COPD based on spirometry data (range between 14.2-42.5 does not necessarily mean that patients did not have COPD at the time of QVA149 initiation as spirometry data for up to five years prior to the index date were considered.

It is unclear why especially in HSD, the proportion (42.5%) of patients for which COPD could not be confirmed by spirometry is high. Spirometry data, as entered by the GP, were reviewed to check whether there was a mix up between FEV_1/FVC ratio and the FEV_1/FVC ratio as percentage of expected. This could only be verified if FEV_1, FVC and FEV_1/FVC ratio were reported. In those patients where these data were available, there was no mix up between FEV_1/FVC ratio and the FEV_1/FVC ratio as percentage of expected. This does not guarantee that spirometry data as entered by the GP are flawless. Also, off-label use in HSD was low with less than 2% of QVA149 initiators using this drug for asthma which contradicts with spirometry findings. No free text validation of COPD was done in this DUS, therefore no information can be provided on the number of QVA149 users for whom COPD diagnosis was confirmed by a specialist.

Information on smoking status was retrieved from all databases, however in contrast to prospective cohort studies, such data are not necessarily collected in a standardized manner. In fact, the proportion of patients with missing data on smoking status was higher in Aarhus (i.e., 41.8%) compared to the other databases (range: 0.0-14.9%). Amongst patients for whom information on smoking status was available, the proportion of never-smokers was highest in SIDIAP (58.6%) compared to the other databases (6.5-17.8%). It is known that smoking is one of the main risk factors of COPD, however, it is estimated that 25-45% of patients with COPD have never smoked. In these patients, passive smoking, in- and outdoor pollution and occupational exposure are considered risk factors for COPD (Salvi and Barnes 2009). Although the proportion of never-smokers among COPD patients is likely to increase over the

coming years, it is difficult to assume that this would only hold for Spain. In addition, the high proportion of COPD in never-smokers is mainly reported in non-European countries. Within the databases that were used in this study, data on smoking is not prospectively collected, The potential for misclassification of smoking, especially between "non-smoking" and "past-smoking", cannot be ruled out. The proportion of patients with missing information on smoking status was the lowest for SIDIAP and THIN and the highest for Aarhus. There is literature suggesting that patients with missing data are more often non-smokers (Marston et al 2014).

In contrast to the Aarhus and SIDIAP databases, the other databases only capture information on prescription and not on dispensing hence potentially leading to misclassification due to primary non-adherence. In addition, it is unknown whether or not the patient actually inhaled the prescribed product; however, as adherence to medicines is highest at initiation of therapy, the risk of misclassification of QVA149-exposure is of lesser concern in a new-user study design such as this one (Lareau and Yawn 2010).

Comorbidities were assessed via disease-specific codes. If disease coding was inconsistent or differential, this could have resulted in diagnostic bias with potential of over and underreporting of comorbidities. Previous validation studies have shown that coding is reliable in the databases being used and that they are suitable for pharmaco-epidemiologic research (Vlug et al 1999; Lewis et al 2007; Ehrenstein et al 2010; Cazzola et al 2011; Garcia-Gil Mdel et al 2011). In contrast to Aarhus, the other databases are primary care database and comorbidities requiring secondary and/or tertiary care such as ischemic heart disease, stroke/TIA, severe cardiac arrhythmia and COPD exacerbations resulting in hospitalization might be underreported. In primary care databases, the incidence and prevalence of comorbidities will depend on physician diagnosis (and coding) and might be underestimated. In contrast, Aarhus retrieves information on disease codes from hospital data (ambulatory care or hospitalized patients). This implies that comorbidities, which do not necessarily require secondary or tertiary care (i.e., arterial hypertension, diabetes mellitus), might be underreported. Finally, as comorbidities were assessed based on disease codes only, there is the potential for underreporting of underlying comorbidity if GPs only record disease symptoms and do not code the corresponding disease.

Differences in underlying co-morbidities were observed between databases. For instance, in HSD and SIDIAP the proportion of patients with a history of angina pectoris and MI was relatively low (3.5% for angina pectoris and 4.8 and 5.4% respectively for myocardial infarction) compared to the other databases (12.2-19.6% for angina pectoris and 7.8-11.1% for myocardial infarction). It is unknown whether or not this is due to real differences in risk of ischemic heart diseases as reported for Mediterranean countries or due to differences in coding and hence potential misclassification (de Lorgeril et al 2002). Also the proportion of patients with BPH was higher in Italy and Spain but this could have been related to differences in gender distribution between the different QVA149 cohorts. Finally, as comorbidities were assessed based on disease codes only, there is the potential of underreporting of underlying comorbidity if GPs only record disease symptoms and do not code the corresponding disease. With regard to switching patterns, up to 64.2% of patients were not using another respiratory drug (long acting bronchodilator with or without ICS) at the time of QVA149 initiation. This would imply that mainly incident COPD patients were studied, however this contradicts our findings pertaining to median duration of COPD and

COPD severity. Upon request by the PRAC, the assessment window was extended to 2 weeks prior to QVA149 initiation. In this analysis, the proportion of patients not using another respiratory drug at the time of QVA149 initiation dropped to 54.4% implying that 1 patient in 2 initiating QVA149 did not use another respiratory drug in the 2 weeks prior to treatment initiation. Exposure windows are calculated assuming that the patient is completely compliant with dosing instructions as provided by the GP but we know from literature that adherence in patients with chronic conditions such as COPD is low (Vetrano et al 2017).

Assessing the number of patients who switched from QVA149 to another respiratory drug was hindered because of short observation time in THIN (47.3%), IPCI (35.4%), Aarhus (40.5%) and HSD (53.8%) i.e., there was not ample time to observe a second prescription of QVA149 for many patients.

Pre-defined thresholds for off-label use, as specified in the RMP, were not exceeded. However, when patients younger than 40 years were studied, the proportion of off-label use increased and was 48.6% for use of QVA149 because of indication “asthma” and 52.6 % for indication asthma or indication COPD & asthma without ICS. As asthma is mainly a disease of the young, it is logical to observe that the proportion of asthma in QVA149 users younger than 40 years increases. Also, the total number of patients younger than 40 years was small (202 patients – 1.4% of total). ICS use was assessed within ± 90 days of the first prescription of QVA149. Calculation of treatment episodes was based on dosing information assuming that the patient is 100% compliant. It is likely to assume that we misclassified exposure to ICS use especially in non-adherent patients.

Finally, interpretation of differences by calendar year was hindered by the fact that the number of patients in 2013 and 2017 was limited. Differences as observed in 2014-2015 vs. 2016 can be explained by differences in database and not necessarily differences over time as 2016 data mainly represent THIN data.

11.3 Interpretation

For this final report, 14,913 new users of QVA149 were identified. From the available data, in relation to the primary objectives, we made the following observations:

The proportion of QVA149 off-label use was mainly driven by use of QVA149 for indication of asthma or indication of asthma/COPD without concomitant use of ICS. However, the pre-defined thresholds in the RMP were not exceeded. The prevalence of asthma in our study population might have been overestimated due to potential misclassification of diagnosis in primary care, where the difficultly to differentiate between asthma and COPD, especially in older patients, is widely accepted ([redacted]). Upon request by the SAC, the duration of asthma in off-label use of QVA149 because of asthma was investigated. The hypothesis was that these patients might first have been recorded as patients with asthma and the diagnosis was later corrected as COPD. If this was the case, the median duration of asthma would be low, as it would coincide with QVA149 initiation (asthma as indication of QVA149-use was only considered if the recorded date of asthma fell within a maximum period of 1 year prior to the index date). The hypothesis was not supported by the data as the median duration of asthma at time of QVA149 initiation was 8.6 years in patients younger than 40 years and 6.9 years in patients 40 years or older.

According to the current label, QVA149 should not be used for the treatment of asthma. In patients with asthma, use of LABA (without concomitant ICS) has been reported to be associated with an increased risk of death. (Nelson et al 2006; Salpeter et al 2006). However, there is growing evidence of a beneficial effect of LAMA in patients with asthma (Anderson, Kew and Boyter 2015; GINA 2017). Use of LABA or LAMA in patients with asthma is only acceptable in case these drugs are combined with an ICS. (Anderson, Kew and Boyter 2015).

With respect to off-label use in terms of age, five of the QVA149 patients were younger than 18 years of age. One patient used QVA149 for asthma, in two of these five patients, the indication of use was not specified, one patient used QVA149 for wheezing and in one patient, the only respiratory code at time of QVA149 prescribing was “nasopharyringitis”. Although QVA149 is not registered for use in patients younger than 18 years of age and should only be used in patients with COPD, as clearly indicated in the product information, this data shows that GPs may not always follow the QVA149 product label in this regard.

Although the number of patients with underlying cerebrovascular and cardiovascular comorbidity was high, it is known from other studies that the prevalence of underlying cardiovascular comorbidity is high in patients with COPD. Indeed, a recent literature review by Smith et al. on comorbidities in patients with COPD reported prevalences estimates of cardiovascular comorbidity (stroke prevalence 7%, heart failure prevalence ranging between 5-24%, ischemic heart disease (AP and MI combined) ranges between 16-53%) (Smith and Wrobel 2014). Both COPD and cardiovascular diseases share the same major risk factors, namely smoking and ageing (Maclay and MacNee 2013; Miller et al 2013) and according to the recent GOLD guidance, COPD is a systemic disease characterized by extra-pulmonary manifestations and comorbidities including cardiovascular disease (GOLD 2017). Overall, our data are in line with previous investigations on comorbidity in patients with COPD and reflect real-life usage.

For those patients where information on serum creatinine or CKD disease stage was available, the proportion of patients with creatinine clearance < 90 mL/min/1.73 m^2 was high. Indeed, 40-50.0% of patients had a clearance between 60-89 mL/min/1.73 m^2 and up to 32% (pooled 17.7%) had a serum creatinine clearance between 30-59 mL/min/1.73 m^2. The proportions observed are consistent with what could be expected in view of the distributions of age and underlying comorbidities (van Blijderveen et al 2013). In addition, overestimation of the proportion of patients with impaired kidney function in this study is a possibility, as not all patients had at least two serum creatinine measurements (i.e., the definition of chronic kidney disease requires a decreased kidney function (eGFR<60 mL/min/1.73 m^2) for at least three months (Levey and Coresh 2012). For all databases the majority of cohort patients were classified as having mild or moderate (CKD stages 2 or 3, respectively) kidney function impairment, while the proportion of patients with severely impaired kidney function and end stage renal failure was low (CKD stages 4 and 5, respectively). These findings are in line with a recent study investigating the prevalence of CKD in patients with COPD also reporting that 31% of patients had an eGFR<60 mL/min/1.73 m^2 (Yoshizawa et al 2015). According to the product information, QVA149 can be used at the recommended dose in patients with mild-to-moderate renal impairment.

The proportion of patients with other underlying co-morbidities of interest namely hepatic impairment (except for THIN and HSD), narrow-angle glaucoma and urinary retention or

symptomatic bladder obstruction was small (<5%). The proportion of patients with BPH and diabetes mellitus was relatively higher. Increased prevalence of diabetes mellitus in COPD patients vs. the general population has been reported in the literature (e.g., Rogliani et al 2014). A frequently cited potential association between ICS exposure and increased risk of incident diabetes or hyperglycemia remains controversial (Faul et al 2009; Slatore, Bryson and Au 2009; Barnes 2010; Rogliani et al 2014).

Two patients were identified as being pregnant during QVA149 use, namely one patient in THIN (UK) and one patient in HSD (IT). The patient in THIN was a 29 year old woman who used QVA149 for asthma with two records of antenatal visits with details that the patient was seen by a midwife. The patient in HSD was a 39 year old woman who used QVA149 for an unknown indication. The outcome of the pregnancies was unknown, but no disease codes for abortion were found in the medical records.

The proportion of patients with mild COPD, assessed via spirometry, was low (4.9-11.3%), which would indicate that QVA149 is being prescribed more to patients with moderate to severe COPD. Use of tri- and tetracyclic antidepressant agents and antipsychotics was elevated and this finding would concur with research showing that depression in COPD patients is relatively common (Garvey 2012).

11.4 Generalizability

This DUS uses real-world data from electronic primary care databases from five European countries. While the large sample size might allow for extrapolation of some of the results to the general population of COPD patients who initiate treatment with QVA149 in various European regions, generalizability may not be appropriate for results for which differences between the databases have been observed such as differences in use of respiratory drugs prior, during and after QVA149 initiation. Observed differences might be database specific but might also be related to differences in health care systems for instance with regard to QVA149 reimbursement where QVA149 can only be prescribed in case monotherapy with a LABA or LAMA was not sufficient.

12 Other information

On 22nd September 2017 a SAC teleconference was held to discuss the final report.

Overall, SAC agreed with the content and the interpretation of the data but suggested minor changes to the limitation and generalizability section of the report which have been implemented.

In addition, they made the following observations. The proportion of patients with a medical history of COPD exacerbation is low (8.0%) which is in line with mild to moderate COPD patients seen in primary care and contrasts with the population included in RCTs which are predominantly performed in secondary care and enrich for frequent exacerbators. Moreover, in 2016, the results of the FLAME trial have been published in the New England Journal of Medicine, demonstrating that QVA149 was superior to ICS/LABA fixed dose combination, in preventing COPD exacerbation in patients with COPD and a history of exacerbations in the previous year. (Wedzicha et al 2016) After the FLAME publication and GOLD 2017 update, it is anticipated that the fixed LABA/LAMA combination will be more often prescribed to

patients with a medical history of COPD exacerbations as this combination is now the preferred initial therapy in GOLD Group D patients (GOLD 2017).

The median duration of QVA149 exposure is low, namely 88 days in the pooled dataset, and it is difficult to conclude whether this is truly means that the patient interrupts treatment with QVA149 or whether this is related to the way treatment episodes are created. To create treatment episodes, a maximum gap of 30 days between prescriptions was accepted irrespective of the duration of the treatment episode. As QVA149 is on the market for a duration of either 30 or 90 days, ideally, the maximum gap would have been defined pro rata of the prescribed treatment duration.

The SAC understands that, as QVA149 is not indicated for the treatment of asthma, all use in patients with asthma is considered as off-label use. However, the safety concern is related to use of QVA149 in asthma patients without concomitant use of ICS.As the proportion of asthma patients, using QVA149 without concomitant use of ICS; was not part of the study objectives, these data are not available.

As discussed during previous SAC meetings, the very high proportion of non-smokers (never-smokers) within the COPD population – i.e. 58.6% - in SIDIAP seems unrealistic. The SAC appreciates that smoking status has been checked in the SIDIAP database and that data reflect what the GP captured in the medical records. Still they believe that there is either a misunderstanding of the definition of non-smokers (never-smokers versus ex-smokers who do not smoke currently), and/or there is missing information on smoking status and smoking history in the SIDIAP database.

With regard to the high number of patients not having COPD based on spirometry data, especially in HSD, the SAC suggested to check for the quality of the curves (both spirogram and flow-volume curves) and whether the measurements within a single patient were reproducible and interpretable (according to ERS/ATS Guidelines on Spirometry). Next, the investigators should double check whether the FEV1/FVC data were presented correctly as ratio and not as percentage predicted. The SAC was informed that it is not possible to check for the quality of the curves and whether measurements are reproducible and interpretable as this information is not available in the database. Also, HSD already checked whether FEV_1/FVC data were correctly presented which was the case.

13 Conclusion

During the study period we identified 14,913 first-time users of inhaled QVA149 with at least one year of valid database history. Off-label use for asthma was 5.5% (pooled dataset) and off-label use in patients with asthma or patients with asthma/COPD without concomitant use of ICS was 7.1%. Pre-defined thresholds for off-label use, as specified in the RMP, were not exceeded. There were 5 patients who were younger than 18 years when initiating QVA149, all within SIDIAP. The pooled overall proportion of off-label use was 14.2 %

The proportion of patients with underlying cardiovascular and cerebrovascular comorbidity was high, and the proportion of QVA149 initiators with high-risk treatment conditions or with conditions defined as ”Missing information” in the Ultibro RMP (e.g., severe or end-stage renal impairment, hepatic impairment, narrow-angle glaucoma, bladder obstruction/urinary retention, pregnant or lactating women) was <5% in the majority of databases.

Results presented in this final study report show that the majority of first-time prescriptions for QVA149 was in line with the product label with regard to dosing, indication of use and age. Proportions of QVA149 patients in subpopulations considered as high-risk treatment conditions or with conditions defined as Missing information in the RMP were in line with prevalence estimates for the COPD population in published literature indicating that QVA149 is considered as treatment option in these patients. Two single QVA149 patients were identified for the subpopulation of pregnant and lactating women suggesting that this population is not treated with QVA149.

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15 Appendices

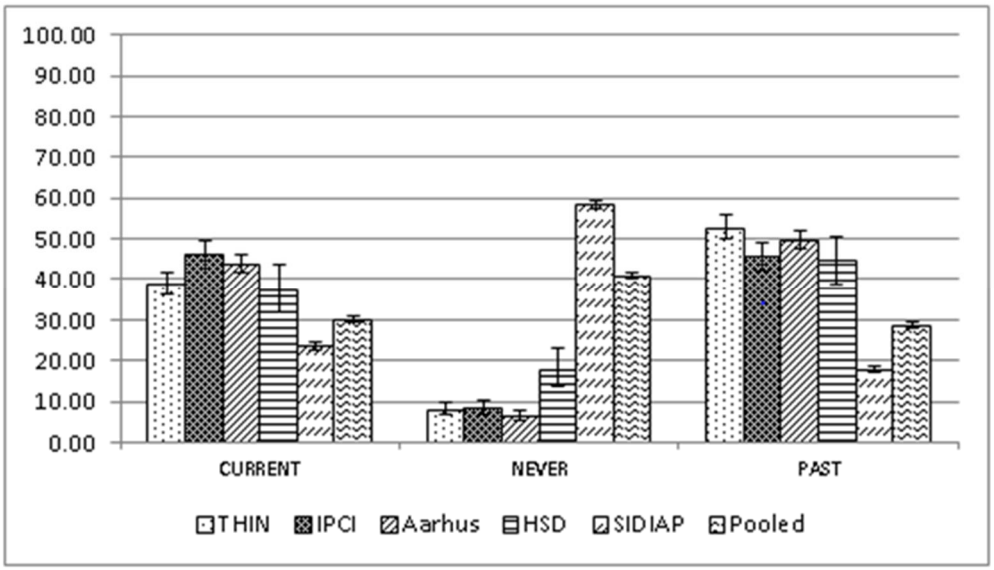
Annex 1 – List of stand-alone documents

There are no stand-alone documents.

Annex 2 – Additional information

Annex 2.1 - Results tables and figures

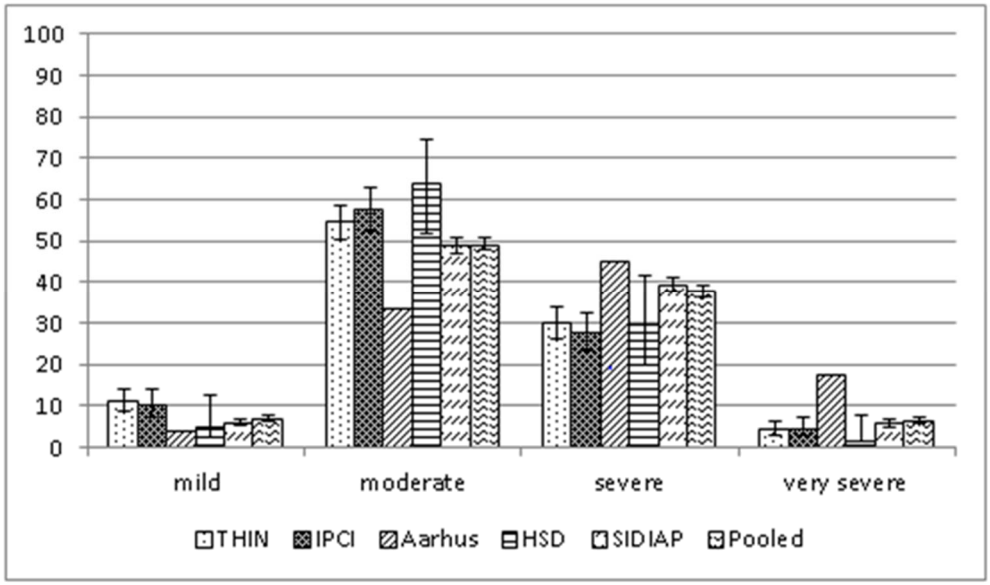
Figure 15-1 Smoking status



⌶ = 95% Confidence interval

Patients with missing information on smoking status excluded from denominator

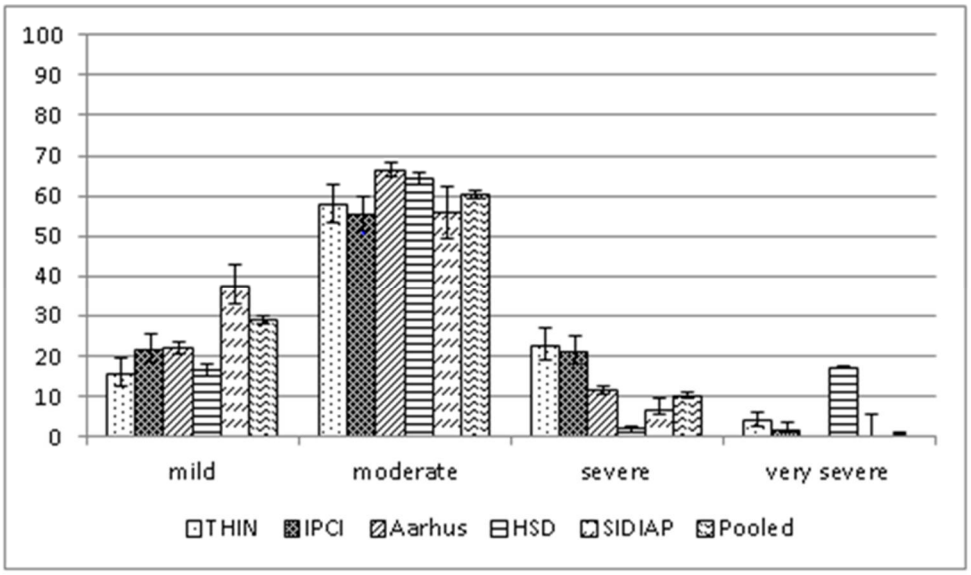
Figure 15-2 COPD severity by spirometry



⌶ = 95% Confidence interval

Patients with missing spirometry data and patients without COPD excluded from the denominator

Figure 15-3 COPD severity by proxy



⊥= 95% Confidence interval

Patients with spirometry data and patients without COPD excluded from the denominator

Figure 15-4 COPD severity based on FEV1% data

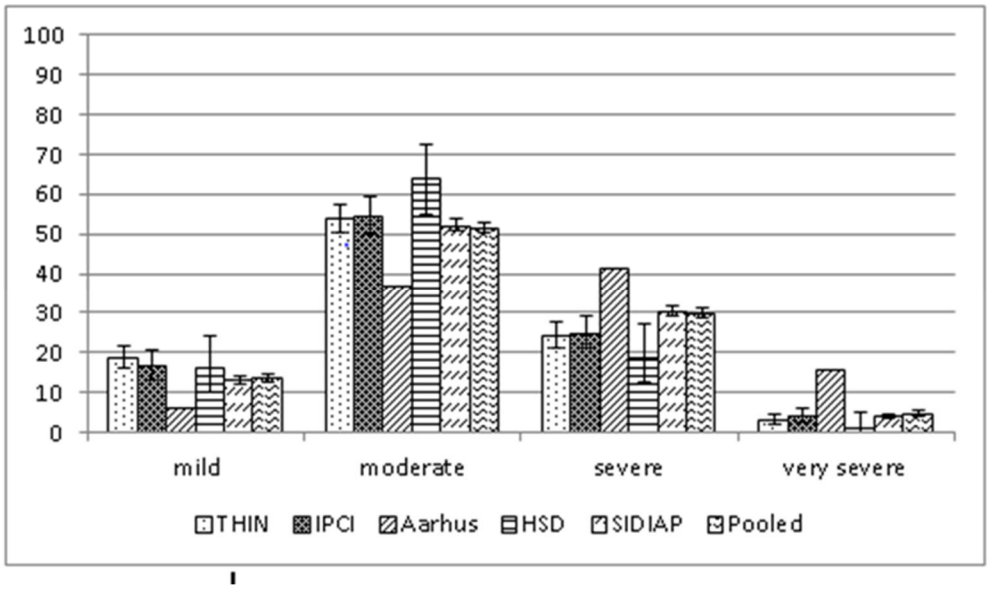
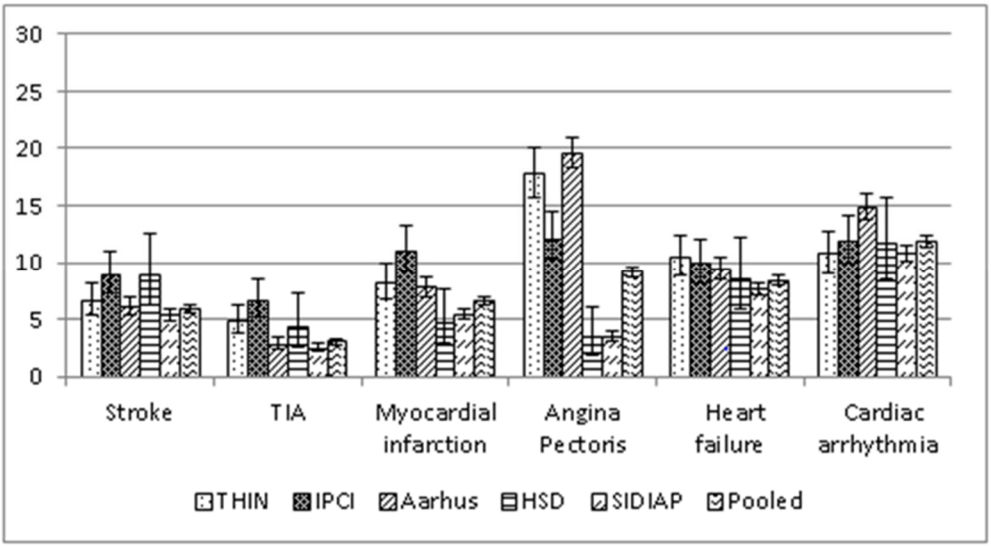
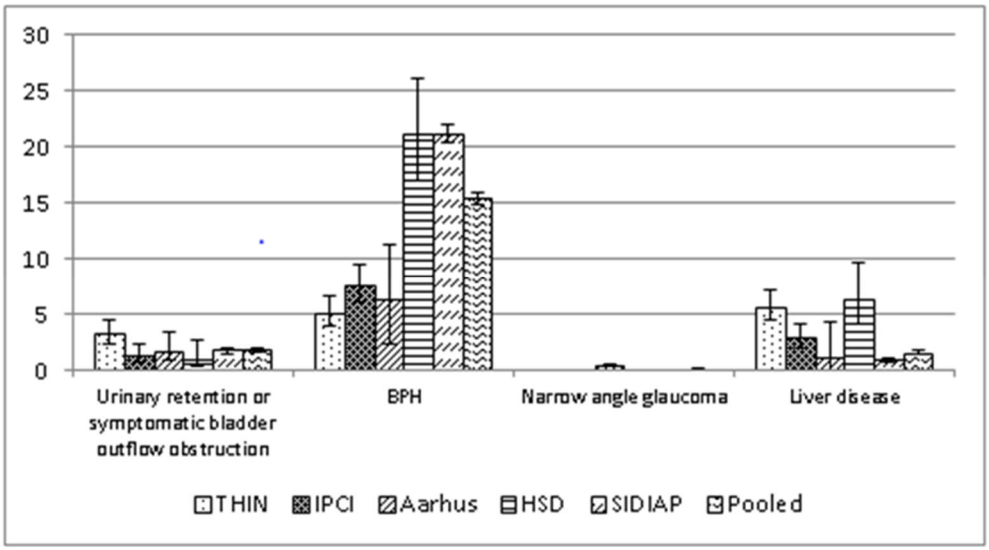


Figure 15-5 Comorbidity in patients with QVA149



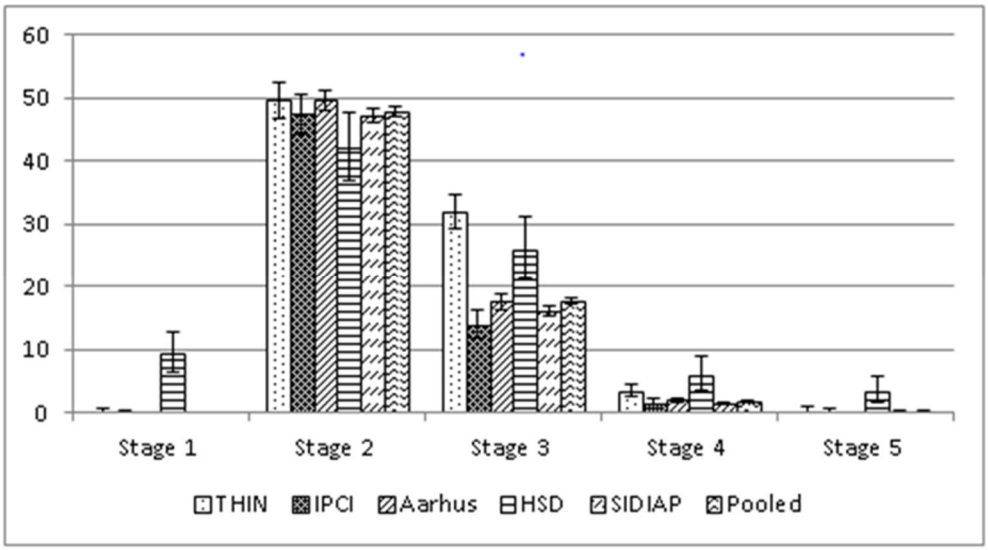
I = 95% Confidence interval

Figure 15-6 Comorbidity in patients with QVA149



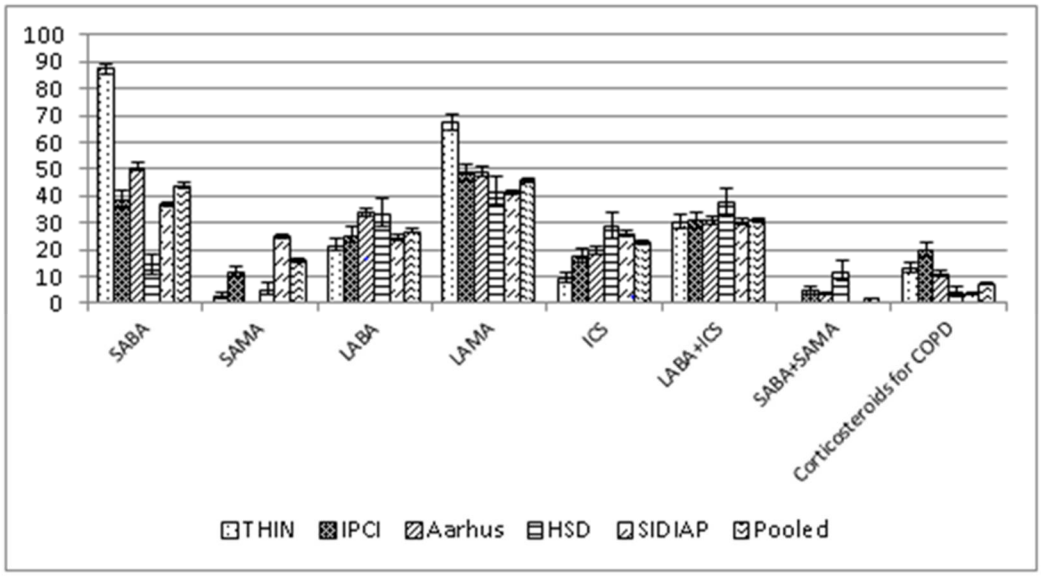
= 95% Confidence interval

Figure 15-7 Chronic kidney disease in patients with QVA149



I = 95% Confidence interval

Figure 15-8 Use of respiratory medications assessed at and within 6 months prior to the index date



I = 95% Confidence interval

Table 15-1 Baseline characteristics of the QVA149 cohort – by calendar year

Characteristic	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI
Database										
THIN	0 (0)	0-3	0 (0)	0-0.07	416 (5.04)	4.59-5.53	733 (99.73)	99.01-99.93	9 (100)	70.09-100
IPCI	46 (37.1)	29.1-45.87	423 (7.3)	6.66-8	459 (5.56)	5.09-6.08	2 (0.27)	0.07-0.99	0 (0)	0-29.91
Aarhus	78 (62.9)	54.13-70.9	1,988 (34.32)	33.11-35.56	1,679 (20.34)	19.49-21.23	0 (0)	0-0.52	0 (0)	0-29.91
HSD	0 (0)	0-3	4 (0.07)	0.03-0.18	312 (3.78)	3.39-4.21	0 (0)	0-0.52	0 (0)	0-29.91
SIDIAP	0 (0)	0-3	3,377 (58.3)	57.03-59.57	5,387 (65.27)	64.24-66.29	0 (0)	0-0.52	0 (0)	0-29.91
Gender										
Female	61 (49.19)	40.55-57.88	2,098 (36.22)	34.99-37.47	2,868 (34.75)	33.73-35.79	358 (48.71)	45.11-52.32	4 (44.44)	18.88-73.34
Male	63 (50.81)	42.12-59.45	3,694 (63.78)	62.53-65.01	5,385 (65.25)	64.21-66.27	377 (51.29)	47.68-54.89	5 (55.56)	26.66-81.12
Age										
<18	0 (0)	0-3	2 (0.03)	0.01- 0.13	3 (0.04)	0.01- 0.11	0 (0)	0-0.52	0 (0)	0-29.91
18 < 40	1 (0.81)	0.14- 4.43	84 (1.45)	1.17- 1.79	111 (1.34)	1.12- 1.62	1 (0.14)	0.02- 0.77	0 (0)	0-29.91
40 < 60	21 (16.94)	11.35-24.51	889 (15.35)	14.44-16.30	1373 (16.64)	15.85-17.46	127 (17.28)	14.72-20.18	1 (11.11)	1.99-43.50
60 - 80	80 (64.52)	55.77-72.39	3,628 (62.64)	61.38-63.88	5048 (61.17)	60.11-62.21	486 (66.12)	62.62-69.45	6 (66.67)	35.42-87.94

Characteristic	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI	n (%)	95 CI
> 80	22 (17.74)	12.02-25.40	1,189 (20.53)	19.51-21.59	1718 (20.82)	19.95-21.71	121 (16.46)	13.96-19.32	2 (22.22)	6.32-54.74
Smoking status										
Missing	34 (27.42)	20.33-35.86	1,001 (17.28)	16.33-18.28	962 (11.66)	10.98-12.37	0 (0)	0-0.52	0 (0)	0-29.91
Current smoker	36 (40.00)	30.49-50.33	1,381 (28.82)	27.56-30.12	2,199 (30.16)	29.12-31.22	279 (37.96)	34.52-41.52	3 (33.33)	12.06-64.58
Past smoker	45 (50.00)	39.88-60.12	1,329 (27.74)	26.49-29.02	1,950 (26.75)	25.74-27.77	387 (52.65)	49.04-56.24	5 (55.56)	26.66-81.12
Never-smoker	9 (10.00)	5.35-17.92	2,081 (43.44)	42.04-44.84	3,142 (43.09)	41.96-44.23	69 (9.39)	7.49-11.71	1 (11.11)	1.99-43.50

CI=confidence interval

Table 15-2 COPD characteristics (assessed at or during the year prior to index date) – by database and pooled

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
COPD severity at index date												
Assessed via spirometry*												
FEV1% Predicted:												
Number (%)	914 (78.93)	76.49-81.18	414 (44.52)	41.35-47.73	1360 (36.32)	34.79-37.87	115 (36.39)	31.28-41.83	4796 (54.72)	53.68-55.76	7599 (50.96)	50.15-51.76
Mean (SD)	62.29 (20.42)		62.63 (20.2)		49.69 (18.12)		65.12 (17.32)		58.64 (18.85)		57.79 (19.4)	
Median (IQR)	61.93 (47.45-75.75)		60.32 (48.45-74.62)		47 (35.04-61)		65 (53-76)		57 (45-70)		56.19 (43.54-70)	
Min-Max	19.35-242.42		8.77-167.69		11.48-184.02		25.9-108		25-125		8.77-242.42	
No. of patients available for analysis of COPD or COPD severity	745 (64.34)	61.53-67.04	410 (44.09)	40.93-47.29	459 (12,26)	11,24-13,35	106 (33,54)	28,56-38,92	4696 (53,58)	52,54-54,63	6416 (43,02)	42,23-43,82
No COPD ($FEV_1/FVC>70$)	186 (24.97%)	21.99-28.20	58 (14.15%)	11.11-17.85	66 (14.38%)	11.46-17.89	45 (42.45%)	33.47-51.96	1437 (30.60%)	29.30-31.93	1792 (27.93%)	26.85-29.04
Mild	63 (11.27)	8.88-14.19	36 (10.23)	7.46-13.85	15 (3.82)	2.35-6.18	3 (4.92)	2.38-12.8	195 (5.98)	5.21-6.87	312 (6.75)	6.05-7.52
Moderate	305 (54.56)	50.35-58.71	203 (57.67)	52.38-62.8	132 (33.59)	29.03-38.47	39 (63.93)	51.54-74.68	1593 (48.88)	47.13-50.63	2272 (49.13)	47.67-50.6
Severe	167 (29.87)	26.17-33.86	97 (27.56)	23.09-32.51	178 (45.29)	40.36-50.31	18 (29.51)	19.74-41.71	1285 (39.43)	37.73-41.15	1745 (37.74)	36.32-39.17
Very severe	24 (4.29)	2.9-6.31	16 (4.55)	2.84-7.23	68 (17.3)	13.84-21.4	1 (1.64)	1.45-7.56	186 (5.71)	4.95-6.57	295 (6.38)	5.7-7.13

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Assessed via proxy**												
No. of patients available for analysis of COPD severity	413 (35.66)	32.91-38.52	520 (55.91)	52.65-59.13	3286 (87.74)	86.63-88.78	210 (66.46)	61.01-71.51	4068 (46.42)	45.35-47.48	8497 (56.98)	56.16-57.79
Mild	64 (15.50)	12.33-19.30	112 (21.54)	18.22-25.27	724 (22.03)	20.65-23.48	35 (16.67%)	12.23-22.30	1523 (37.44%)	35.96-38.94	2458 (28.93%)	27.97-29.90
Moderate	240 (58.11)	53.30-62.77	289 (55.58)	51.28-59.79	2184 (66.46)	64.83-68.06	135 (64.29%)	57.60-70.46	2274 (55.90%)	54.37-57.42	5122 (60.28%)	59.24-61.32
Severe	93 (22.52)	18.75-26.79	110 (21.15)	17.86-24.87	378 (11.50)	10.46-12.64	4 (1.90%)	0.74- 4.79	271 (6.66%)	5.94- 7.47	856 (10.07%)	9.45-10.73
Very Severe	16 (3.87)	2.40- 6.20	9 (1.73)	0.91- 3.26	0 (0)	0-0.12	36 (17.14%)	12.65-22.82	0 (0)	0-0.09	61 (0.72%)	0.56-0.92
COPD severity irrespective of FEV1/FVC ratio												
Total number of patients considered for analysis	745 (64.34)	61.53-67.04	410 (44.09)	40.93-47.29	459 (12.26)	11.24-13.35	106 (33.54)	28.56-38.92	4,696 (53.58)	52.54-54.63	6,416 (43.02)	42.23-43.82
Mild	139 (18.66)	16.02-21.61	68 (16.59)	13.30-20.49	28 (6.10)	4.25-8.68	17 (16.04)	10.26-24.19	622 (13.25)	12.31-14.24	874 (13.62)	12.8-14.48
Moderate	401 (53.83)	50.24-57.38	224 (54.63)	49.79-59.39	168 (36.60)	32.32-41.10	68 (64.15)	54.67-72.64	2,450 (52.17)	50.74-53.60	3,311 (51.61)	50.38-52.83
Severe	181 (24.30)	21.35-27.50	102 (24.88)	20.94-29.28	190 (41.39)	36.98-45.95	20 (18.87)	12.56-27.35	1,433 (30.52)	29.21-31.85	1,926 (30.02)	28.91-31.15
Very Severe	24 (3.22)	2.17-4.75	16 (3.90)	2.42-6.24	73 (15.90)	12.84-19.53	1 (0.94)	0.17-5.15	191 (4.07)	3.54-4.67	305 (4.75)	4.26-5.3

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
No. of COPD exacerbations requiring hospitalization in the one year prior to the index date												
Mean (SD)	0.15 (0.45)		0.1 (0.39)		0.18 (0.68)		0 (0)		0.1 (0.45)		0.12 (0.51)	
Median (IQR)	0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)	
Min-max	0-6		0-3		0-10		0-0		0-11		0-11	
COPD exacerbations requiring hospitalization in the year prior to index date												
None	1011 (87.31)	85.26-89.10	861 (92.58)	90.72-94.10	3346 (89.35)	88.32-90.29	316 (100.0%)	98.80-100.0	8166 (93.18%)	92.63-93.69	13700 (91.87%)	91.42-92.29
1	123 (10.62)	8.98-12.53	51 (5.48)	4.20- 7.14	247 (6.60)	5.84- 7.44	0 (0)	0-1.2	429 (4.90%)	4.46- 5.37	850 (5.70%)	5.34-6.08
2	21 (1.81)	1.19- 2.76	12 (1.29)	0.74- 2.24	86 (2.30)	1.86- 2.83	0 (0)	0-1.2	117 (1.34%)	1.12- 1.60	236 (1.58%)	1.39-1.80
3 or more	3 (0.26)	0.09- 0.76	6 (0.65)	0.30- 1.40	66 (1.76)	1.39- 2.24	0 (0)	0-1.2	52 (0.59%)	0.45- 0.78	127 (0.85%)	0.72-1.01
Number of systemic steroid episodes for the treatment of COPD in the year prior to index date												
0	939 (81.09)	78.73-83.24	693 (74.52)	71.62-77.21	3258 (87.00)	85.88-88.04	300 (94.94%)	91.93-96.86	8362 (95.41%)	94.95-95.83	13552 (90.87%)	90.40-91.33
1	181 (15.63)	13.65-17.84	153 (16.45)	14.21-18.97	418 (11.16)	10.19-12.21	15 (4.75%)	2.90- 7.68	378 (4.31%)	3.91- 4.76	1145 (7.68%)	7.26-8.12
2	28 (2.42)	1.68- 3.47	63 (6.77)	5.33- 8.57	54 (1.44)	1.11- 1.88	1 (0.32%)	0.06- 1.77	23 (0.26%)	0.17- 0.39	169 (1.13%)	0.98-1.32

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
3 or more	10 (0.86)	0.47- 1.58	21 (2.26)	1.48- 3.43	15 (0.40)	0.24- 0.66	0 (0)	0-1.2	1 (0.01%)	0.00- 0.06	47 (0.32%)	0.24- 0.42
Number of antibiotic courses for treatment of COPD exacerbations/LRTI in the year prior to index date												
0	906 (78.24)	75.77- 80.52	617 (66.34)	63.25- 69.31	3074 (82.08)	80.82- 83.28	275 (87.03%)	82.87- 90.29	7340 (83.75%)	82.96- 84.51	12212 (81.89%)	81.26- 82.50
1	161 (13.90)	12.03- 16.02	185 (19.89)	17.45- 22.58	429 (11.46)	10.47- 12.52	30 (9.49%)	6.73-13.23	958 (10.93%)	10.29- 11.60	1763 (11.82%)	11.31- 12.35
2	62 (5.35)	4.20- 6.80	82 (8.82)	7.16- 10.81	145 (3.87)	3.30- 4.54	7 (2.22%)	1.08- 4.50	343 (3.91%)	3.53- 4.34	639 (4.28%)	3.97- 4.62
3 or more	29 (2.50)	1.75- 3.57	46 (4.95)	3.73- 6.53	97 (2.59)	2.13- 3.15	4 (1.27%)	0.49- 3.21	123 (1.40%)	1.18- 1.67	299 (2.00%)	1.79- 2.24
Duration of COPD (years)												
Mean (SD)	6.36 (6.35)		6.06 (5.63)		5.35 (5.19)		6.47 (4.85)		6.42 (5.73)		6.15 (5.68)	
Median (IQR)	4.53 (1.62-9.07)		4.87 (1.98-8.21)		3.77 (1.03-8.49)		6.35 (1.78-10.37)		5.03 (1.84-9.73)		4.74 (1.65-9.38)	
Min-max	0-46.04		0-45.06		0-21.03		0-15.73		0-49.91		0-49.91	
Duration of asthma (years)												
Mean (SD)	15.54 (10.36)		7.52 (5.32)		10.64 (6.41)		8.46 (4.7)		8.63 (7.67)		9.83 (7.95)	
Median (IQR)	14.53 (7.2-21.85)		6.77 (3.36-10.27)		10.74 (5.09-16.15)		9.01 (4.89-12.96)		7.55 (2.98-11.29)		8.72 (4.07-13.6)	
Min-max	0.02-49.8		0-23.27		0-21.87		0.07-15.74		0-49.8		0-49.8	

*Subset of patients for which spirometry data were available (i.e., both FEV1% and FVC values available); ** Subset of patients for which COPD severity was assessed via proxy;
CI=confidence interval; SD=standard deviation; IQR=Interquartile range; n.a.= not available

Table 15-3 Prescribed dosage of QVA149 assessed at index date, duration of use and number of patients who used QVA149 for more than 1 year, by database and pooled

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Prescribed dosage of QVA149 at index date:	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Missing	0 (0)	0-0.33	13 (1.40%)	0.82- 2.38	3,745 (100.0%)	99.90-100.0	0 (0)	0-1.2	8,764 (100.0%)	99.96-100.0	12,522 (83.97)	83.37-84.55
Once daily*	1,149 (99.22%)	98.53-99.59	907 (98.91)	98-99.41	n.a.	n.a.	313 (99.05%)	97.25-99.68	n.a.	n.a.	2,369 (99.08)	98.61-99.39
Every other day*	0 (0)	0-0.33	0 (0)	0-0.42	n.a.	n.a.	0 (0)	0-1.20	n.a.	n.a.	0 (0)	0-0.16
Twice daily*	0 (0)	0-0.33	9 (0.98)	0.52-1.85	n.a.	n.a.	3 (0.95%)	0.32- 2.75	n.a.	n.a.	12 (0.5)	0.29-0.88
Other*	9 (0.78%)	0.41- 1.47	1 (0.11)	0.02-0.62	n.a.	n.a.	0 (0)	0-1.20	n.a.	n.a.	10 (0.42)	0.23-0.77
Median duration of QVA149 (min-max) (days)	98 (1-695)		91 (1-791)		115 (1-764)		60 (1-227)		60 (2-608)		88 (1-791)	
Patients who used QVA149 for more than 1 year	142 (12.00)	10.50-14.28	113 (12.00)	10.21-14.41	693 (18.00)	17.29-19.78	0 (0)	0-1.20	560 (6.00)	5.90-6.92	1508 (10.11%)	9.64-10.61

Patients who use QVA149 for more than 1.5 year	31 (2.00)	1.89-3.77	38 (4.00)	2.99-5.56	309 (8.00)	7.41-9.18	0 (0)	0-1.20	88 (1.00)	0.82-1.24	466 (3.12)	2.86-3.42

*Percentages in number of patients for whom dosage is known; n.a.= not available.

Table 15-4 Prescribed dosage of QVA149 assessed at index date, duration of use and number of patients who used QVA149 for more than 1 year, by calendar year

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Prescribed dosage of QVA149 at index date:	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Missing	78 (62.9)	54.13-70.9	5369 (92.7)	92-93.34	7075 (85.73)	84.96-86.46	0 (0)	0-0.52	0 (0)	0-29.91
Once daily*	45 (97.83)	88.66-99.62	421 (99.53)	98.29-99.87	1168 (99.15)	98.44-99.54	726 (98.78%)	97.69-99.35	9 (100.0%)	70.08-100.0
Every other day*	0 (0)	0-7.71	0 (0)	0-0.9	0 (0)	0-0.33	9 (1.22%)	0.65- 2.31	0 (0)	0-29.91
Twice daily*	1 (2.17)	0.38-11.34	2 (0.47)	0.13-1.71	9 (0.76)	0.4-1.45	0 (0)	0-0.52	0 (0)	0-29.91
Other*	0 (0)	0-7.71	0 (0)	0-0.9	1 (0.08)	0.01-0.48	0 (0)	0-0.52	0 (0)	0-29.91
Median duration of QVA149 (min-max) (days)	137 (24-791)		117 (2-725)		60 (1-695)		79 (6-368)		1 (1-2)	
Patients who used QVA149 for more than 1 year	45 (36.29%)	28.36-45.05	1319 (22.77%)	21.71-23.87	141 (1.71%)	1.45- 2.01	3 (0.41%)	0.14- 1.19	0 (0.00%)	0.00-29.92
Patients who use QVA149 for more than 1.5 year	38 (30.65)	23.21-39.24	397 (6.85)	6.23-7.53	31 (0.38)	0.26-0.53	0 (0)	0-0.52	0 (0.00%)	0.00-29.92

*Percentages in number of patients for whom dosage is known; n.a.= not available.

Table 15-5 Switching from other respiratory drugs to QVA149 (assessed on index date) by database and pooled

Switching from other respiratory drugs to QVA149	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA	50 (4.32)	3.29- 5.65	52 (5.59)	4.29- 7.26	387 (10.33)	9.40- 11.35	25 (7.91)	5.42- 11.42	371 (4.23)	3.83- 4.68	885 (5.93)	5.57- 6.33
LAMA	260 (22.45)	20.14- 24.94	113 (12.15)	10.20- 14.41	387 (10.33)	9.40- 11.35	22 (6.96)	4.64- 10.32	444 (5.07)	4.63- 5.55	1226 (8.22)	7.79- 8.67
LABA/LAMA	141 (12.18)	10.42- 14.19	50 (5.38)	4.10- 7.02	240 (6.41)	5.67- 7.24	11 (3.48)	1.95- 6.12	275 (3.14)	2.79- 3.52	717 (4.81)	4.48- 5.16
LABA/ICS	88 (7.60)	6.21- 9.27	90 (9.68)	7.94- 11.75	406 (10.84)	9.89- 11.88	40 (12.66)	9.44- 16.78	637 (7.27)	6.74- 7.83	1261 (8.46)	8.02- 8.91
LAMA/ICS	13 (1.12)	0.66- 1.91	17 (1.83)	1.14- 2.91	54 (1.44)	1.11- 1.88	3 (0.95)	0.32- 2.75	43 (0.49)	0.36- 0.66	130 (0.87)	0.73- 1.03
LABA/LAMA/ICS	148 (12.78)	10.98- 14.83	112 (12.04)	10.11- 14.29	408 (10.89)	9.94- 11.93	20 (6.33)	4.13- 9.57	435 (4.96)	4.53- 5.44	1123 (7.53)	7.12- 7.96
No use of other respiratory drugs	458 (39.55)	36.77- 42.40	496 (53.33)	50.12- 56.52	1863 (49.75)	48.15- 51.35	195 (61.71)	56.24- 66.90	6559 (74.84)	73.92- 75.74	9571 (64.18)	63.41- 64.94

Table 15-6 Switching from other respiratory drugs to QVA149 (assessed on index date) by calendar year

Switching from other respiratory drugs to QVA149	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA	16 (12.90)	8.10-19.94	418 (7.22)	6.58- 7.91	430 (5.21)	4.75- 5.71	21 (2.86)	1.88- 4.33	0 (0)	0-29.91
LAMA	12 (9.68)	5.62-16.16	438 (7.56)	6.91- 8.27	617 (7.48)	6.93- 8.06	157 (21.36)	18.55-24.47	2 (22.22)	6.32-54.74
LABA/LAMA	14 (11.29)	6.85-18.06	326 (5.63)	5.06- 6.25	294 (3.56)	3.18- 3.98	82 (11.16)	9.08-13.64	1 (11.11)	1.99-43.50
LABA/ICS	16 (12.90)	8.10-19.94	559 (9.65)	8.92-10.44	630 (7.63)	7.08- 8.23	55 (7.48)	5.79- 9.61	1 (11.11)	1.99-43.50
LAMA/ICS	5 (4.03)	1.73- 9.09	60 (1.04)	0.81- 1.33	55 (0.67)	0.51- 0.87	10 (1.36)	0.74- 2.49	0 (0)	0-29.91
LABA/LAMA/ICS	25 (20.16)	14.05-28.07	493 (8.51)	7.82- 9.26	508 (6.16)	5.66- 6.69	97 (13.20)	10.94-15.84	0 (0)	0-29.91
No use of other respiratory drugs	36 (29.03)	21.77-37.56	3498 (60.39)	59.13-61.65	5719 (69.30)	68.29-70.28	313 (42.59)	39.06-46.19	5 (55.56)	26.66-81.12

Table 15-7 Switching from other respiratory drugs to QVA149 (assessed in 14 days prior to the index date) by database and pooled

Switching from other respiratory drugs to QVA149	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA	52 (4.49)	3.44-5.84	52 (5.59)	4.29-7.26	381 (10.17)	9.25-11.18	33 (10.44)	7.53-14.30	434 (4.95)	4.52-5.43	952 (6.38)	6-6.79
LAMA	285 (24.61)	22.22-27.17	115 (12.37)	10.40-14.64	433 (11.56)	10.58-12.63	19 (6.01)	3.88-9.20	549 (6.26)	5.78-6.79	1401 (9.39)	8.94-9.87
LABA/LAMA	155 (13.39)	11.54-15.47	62 (6.67)	5.24-8.45	333 (8.89)	8.02-9.85	13 (4.11)	2.42-6.91	465 (5.31)	4.86-5.79	1028 (6.89)	6.5-7.31
LABA/ICS	92 (7.94)	6.52-9.65	93 (10.00)	8.23-12.10	422 (11.27)	10.30-12.32	54 (17.09)	13.34-21.63	914 (10.43)	9.81-11.09	1575 (10.56)	10.08-11.06
LAMA/ICS	16 (1.38)	0.85-2.23	18 (1.94)	1.23-3.04	60 (1.60)	1.25-2.06	2 (0.63)	0.17-2.28	74 (0.84)	0.67-1.06	170 (1.14)	0.98-1.32
LABA/LAMA/ICS	184 (15.89)	13.90-18.11	135 (14.52)	12.40-16.93	558 (14.90)	13.80-16.08	26 (8.23)	5.68-11.78	772 (8.81)	8.23-9.42	1675 (11.23)	10.73-11.75
No use of other respiratory drugs	374 (32.30)	29.67-35.05	455 (48.92)	45.72-52.14	1558 (41.60)	40.03-43.19	169 (53.48)	47.97-58.91	5556 (63.40)	62.38-64.40	8112 (54.4)	53.6-55.19

Table 15-8 Switching from other respiratory drugs to QVA149 (assessed in 14 days prior to the index date) by calendar year

Switching from other respiratory drugs to QVA149	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA	15 (12.10)	7.47-19.00	412 (7.11)	6.48- 7.80	501 (6.07)	5.58- 6.61	24 (3.27)	2.20- 4.81	0 (0)	0-29.91
LAMA	12 (9.68)	5.62-16.16	518 (8.94)	8.24- 9.71	695 (8.42)	7.84- 9.04	174 (23.67)	20.74-26.88	2 (22.22)	6.32-54.74
LABA/LAMA	17 (13.71)	8.74-20.86	507 (8.75)	8.05- 9.51	418 (5.06)	4.61- 5.56	85 (11.56)	9.45-14.08	1 (11.11)	1.99-43.50
LABA/ICS	16 (12.90)	8.10-19.94	655 (11.31)	10.52-12.15	849 (10.29)	9.65-10.96	54 (7.35)	5.67- 9.46	1 (11.11)	1.99-43.50
LAMA/ICS	5 (4.03)	1.73- 9.09	72 (1.24)	0.99- 1.56	82 (0.99)	0.80- 1.23	11 (1.50)	0.84- 2.66	0 (0)	0-29.91
LABA/LAMA/ICS	29 (23.39)	16.81-31.57	739 (12.76)	11.92-13.64	784 (9.50)	8.89-10.15	123 (16.73)	14.21-19.60	0 (0)	0-29.91
No use of other respiratory drugs	30 (24.19)	17.50-32.43	2889 (49.88)	48.59-51.17	4924 (59.66)	58.60-60.72	264 (35.92)	32.53-39.45	5 (55.56)	26.66-81.12

Table 15-9 Add-on therapy (assessed on index date) by database and pooled

Add-on therapy	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA	3 (0.26)	0.09- 0.76	14 (1.51)	0.90- 2.51	63 (1.68)	1.32- 2.15	4 (1.27)	0.49- 3.21	219 (2.50)	2.19- 2.85	303 (2.03)	1.82- 2.27
LAMA	28 (2.42)	1.68- 3.47	17 (1.83)	1.14- 2.91	38 (1.01)	0.74- 1.39	4 (1.27)	0.49- 3.21	28 (2.42)	1.68- 3.47	360 (2.41)	2.18- 2.67
LABA/LAMA	9 (0.78)	0.41- 1.47	7 (0.75)	0.37- 1.55	20 (0.53)	0.35- 0.82	2 (0.63)	0.17- 2.28	133 (1.52)	1.28- 1.80	171 (1.15)	0.99- 1.33
LABA/ICS	15 (1.30)	0.79- 2.13	33 (3.55)	2.54- 4.94	157 (4.19)	3.60- 4.88	9 (2.85)	1.51- 5.32	743 (8.48)	7.91- 9.08	957 (6.42)	6.04- 6.82
LAMA/ICS	4 (0.35)	0.13- 0.88	2 (0.22)	0.06- 0.78	9 (0.24)	0.13- 0.46	0 (0)	0-1.2	77 (0.88)	0.70- 1.10	92 (0.62)	0.50- 0.76
LABA/LAMA/ICS	21 (1.81)	1.19- 2.76	19 (2.04)	1.31- 3.17	51 (1.36)	1.04- 1.79	3 (0.95)	0.32- 2.75	324 (3.70)	3.32- 4.11	418 (2.80)	2.55- 3.08
No use of other respiratory drugs	1,078 (93.09)	91.48- 94.41	838 (90.11)	88.02- 91.86	3407 (90.97)	90.01- 91.85	294 (93.04)	89.68- 95.36	6,995 (79.82)	78.96- 80.64	12,612 (84.57)	83.98- 85.14

Table 15-10 Add-on therapy (assessed on index date) by calendar year

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Add-on therapy	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
LABA	2 (1.61)	0.44- 5.69	163 (2.81)	2.42- 3.27	135 (1.64)	1.38- 1.93	3 (0.41)	0.14- 1.19	0 (0)	0-29.91
LAMA	3 (2.42)	0.83- 6.87	145 (2.50)	2.13- 2.94	197 (2.39)	2.08- 2.74	15 (2.04)	1.24- 3.34	0 (0)	0-29.91
LABA/LAMA	1 (0.81)	0.14- 4.43	77 (1.33)	1.07- 1.66	90 (1.09)	0.89- 1.34	3 (0.41)	0.14- 1.19	0 (0)	0-29.91
LABA/ICS	7 (5.65)	2.76- 11.19	446 (7.70)	7.04- 8.42	497 (6.02)	5.53- 6.56	7 (0.95)	0.46- 1.95	0 (0)	0-29.91
LAMA/ICS	0 (0)	0-3	40 (0.69)	0.51- 0.94	50 (0.61)	0.46- 0.80	2 (0.27)	0.07- 0.99	0 (0)	0-29.91
LABA/LAMA/ICS	2 (1.61)	0.44- 5.69	176 (3.04)	2.63- 3.51	223 (2.70)	2.37- 3.07	17 (2.31)	1.45- 3.67	0 (0)	0-29.91
No use of other respiratory drugs	109 (87.90)	81.00- 92.53	4,745 (81.92)	80.91- 82.89	7,061 (85.56)	84.78- 86.30	688 (93.61)	91.60- 95.16	9 (100.0)	70.08- 100.0

Table 15-11 Switching from QVA149 to other respiratory drugs (assessed at end of QVA149 treatment) by database and pooled

Switch from QVA149 to:	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA[#]	10 (1.64)	0.92-2.96	15 (2.5)	1.53-4.06	101 (4.53)	3.73-5.49	6 (4.11)	2.08-8.49	118 (1.39)	1.16-1.67	250 (2.07)	1.83-2.35
LAMA[#]	29 (4.75)	3.32-6.75	40 (6.66)	4.91-8.95	102 (4.57)	3.77-5.54	5 (3.42)	1.69-7.55	158 (1.86)	1.59-2.18	334 (2.77)	2.48-3.08
LABA/LAMA[#]	49 (8.03)	6.11-10.48	29 (4.83)	3.38-6.85	87 (3.9)	3.16-4.8	6 (4.11)	2.08-8.49	61 (0.72)	0.56-0.93	232 (1.92)	1.69-2.19
LABA/ICS[#]	34 (5.57)	4.01-7.7	60 (9.98)	7.81-12.67	201 (9.01)	7.87-10.29	9 (6.16)	3.41-11.17	462 (5.45)	4.98-5.96	766 (6.35)	5.92-6.81
LAMA/ICS[#]	6 (0.98)	0.5-2.08	5 (0.83)	0.41-1.88	23 (1.03)	0.69-1.54	0 (0)	1.28-1.28	30 (0.35)	0.25-0.51	64 (0.53)	0.41-0.68
LABA/LAMA/ICS[#]	74 (12.13)	9.74-15	44 (7.32)	5.48-9.7	190 (8.52)	7.41-9.77	7 (4.79)	2.51-9.4	204 (2.41)	2.1-2.76	519 (4.3)	3.95-4.69
No use of other respiratory drugs[#]	408 (66.89)	62.99-70.57	408 (67.89)	63.99-71.56	1,526 (68.43)	66.43-70.36	113 (77.4)	69.95-83.44	7,444 (87.81)	87.09-88.51	9,899 (82.05)	81.35-82.74
Undefined	548 (47.32)	44.46-50.20	329 (35.38)	32.37-38.50	1,515 (40.45)	38.89-42.03	170 (53.80)	48.29-59.22	287 (3.27)	2.92-3.67	2,849 (19.10%)	18.48-19.74

[#]: excluding number of patients where switching could not be defined from denominator

Table 15-12 Switching from QVA149 to other respiratory drugs (assessed at end of QVA149 treatment) by calendar year

Switch from QVA149 to:	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
LABA[#]	5 (5.81)	2.87-12.53	123 (2.45)	2.05-2.93	117 (1.76)	1.47-2.11	5 (1.51)	0.74-3.39	0 (0)	0-29.91
LAMA[#]	4 (4.65)	2.24-10.94	152 (3.03)	2.59-3.55	169 (2.55)	2.19-2.96	9 (2.72)	1.49-5.03	0 (0)	0-29.91
LABA/LAMA[#]	3 (3.49)	1.69-9.27	98 (1.96)	1.6-2.38	97 (1.46)	1.2-1.78	34 (10.27)	7.43-14.03	0 (0)	0-29.91
LABA/ICS[#]	10 (11.63)	6.65-19.89	353 (7.04)	6.35-7.8	381 (5.74)	5.2-6.34	22 (6.65)	4.44-9.85	0 (0)	0-29.91
LAMA/ICS[#]	2 (2.33)	1.25-7.48	34 (0.68)	0.48-0.95	23 (0.35)	0.23-0.52	5 (1.51)	0.74-3.39	0 (0)	0-29.91
LABA/LAMA/ICS[#]	11 (12.79)	7.49-21.28	231 (4.61)	4.05-5.24	238 (3.59)	3.16-4.07	39 (11.78)	8.72-15.72	0 (0)	0-29.91
No use of other respiratory drugs[#]	51 (59.3)	48.76-69.05	4,020 (80.22)	79.08-81.32	5,611 (84.55)	83.65-85.42	217 (65.56)	60.22-70.54	0 (0)	0-29.91
Undefined	38 (30.65)	23.21-39.24	781 (13.48)	12.63-14.39	1,617 (19.59)	18.75-20.46	404 (54.97)	51.35-58.53	9 (100.0)	70.08-100.0

[#]: excluding number of patients where switching could not be defined from denominator

Table 15-13 QVA149 – off-label use (by database and pooled) – missing excluded from all denominators

		THIN [UK] (N=1,158)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,745)			HSD [IT] (N=316)			SIDIAP [ES] (N=8,764)			Pooled Data (N=14,913)		
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
Off-label because of indication asthma																			
	Yes	26 (2.31)	1.58-3.36	<0.0001	35 (3.78)	2.73-5.21	<0.0001	44 (1.89)	1.41-2.52	<0.0001	3 (1.36)	0.46-3.91	<0.0001	595 (7.24)	6.70-7.83	0.00260	703 (5.48)	5.1-5.89	<0.0001
	No	1100 (97.69)	96.64-98.42		892 (96.22)	94.79-97.27		2288 (98.11)	97.48-98.59		218 (98.64)	96.09-99.54		7,627 (92.86)	92.29-93.40		12125 (94.52)	94.11-94.9	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.95		1413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2085 (13.98)	13.43-14.55	
Off-label because of indication asthma or indication COPD & asthma without ICS																			
				P> 15%			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**
	Yes	81 (7.19)	5.83-8.85	<0.0001	61 (6.58)	5.16-8.36	<0.0001	58 (2.49)	1.93-3.20	<0.0001	4 (1.81)	0.71-4.56	<0.0001	705 (8.58)	8.00-9.21	<0.0001	909 (7.09)	6.65-7.54	<0.0001
	No	1045 (92.81)	91.15-94.17		866 (93.42)	91.64-94.84		2274 (97.55)	96.85-98.11		217 (98.19)	95.44-99.29		7,517 (91.53)	90.90-92.11		11,919 (92.91)	92.46-93.35	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.95		1413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2,085 (13.98)	13.43-14.55	
Off-label because of indication 'other'																			
	Yes	58 (5.15)	4.01-6.6		28 (3.02)	2.1-4.33		43 (1.84)	1.37-2.47		4 (1.81)	0.71-4.56		1,080 (13.14)	12.42-13.88		1,213 (9.46)	8.96-9.97	

		THIN [UK] (N=1,158)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,745)			HSD [IT] (N=316)			SIDIAP [ES] (N=8,764)			Pooled Data (N=14,913)		
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
	No	1068 (94.85)	93.4-95.99		899 (96.98)	95.67-97.9		2289 (98.16)	97.53-98.63		217 (98.19)	95.44-99.29		7,142 (86.86)	86.12-87.58		11,615 (90.54)	90.03-91.04	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.94		1413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		542 (6.60)	6.08-7.16		2,085 (13.98)	13.43-14.55	
Off-label because of age																			
	Yes	0 (0)	0-0.33		0 (0)	0-0.41		0 (0)	0-0.1		0 (0)	0-1.2		5 (0.06)	0.02-0.13		5 (0.03)	0.01-0.08	
	No	1158 (100.0)	99.67-100.0		930 (100.00)	99.59-100.00		3,745 (100.00)	99.90-100.00		316 (100.00)	98.80-100.00		8,759 (99.94)	99.87-99.98		14,908 (99.97)	99.92-99.99	
Off-label total																			
	Yes	139 (12.34)	10.55-14.39		89 (9.6)	7.87-11.67		101 (4.33)	3.58-5.24		8 (3.62)	1.85-6.98		1,787 (21.73)	20.85-22.63		2,124 (16.55)	15.92-17.21	
	No	987 (87.66)	85.61-89.45		838 (90.4)	88.33-92.13		2231 (95.67)	94.76-96.42		213 (96.38)	93.02-98.15		6,437 (78.27)	77.37-79.15		10,706 (83.45)	82.79-84.08	
	Missing	32 (2.76)	1.96-3.88		3 (0.32)	0.11-0.94		1413 (37.73)	36.19-39.29		95 (30.06)	25.27-35.33		540 (6.16)	5.68-6.68		2,083 (13.97)	13.42-14.53	

CI=Confidence interval

Table 15-14 QVA149 – off-label use (by database and pooled) – stratified in patients <40 and >= 40 years

		THIN [UK] (N=7)			IPCI [NL] (N=1)			Aarhus [DK] (N=17)			HSD [IT] (N=1)			SIDIAP [ES] (N=167)			Pooled Data (N=202)		
<40 Years																			
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
Off-label because of indication asthma#¥																			
	Yes	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	79 (50.32)	42.58-58.04	1.00000	85 (48.57)	41.28-55.93	1.00000
	No	Nap			Nap			Nap			Nap			78 (49.68)	41.96-57.42		90 (51.43)	44.07-58.72	
	Missing	Nap			Nap			Nap			Nap			19 (11.38)	7.41-17.09		27 (13.37)	9.35-18.75	
Duration of asthma in patients who use QVA149 off-label because of asthma Median - IQR		Nap			Nap			Nap			Nap			8.63 (2.79-11.07)			8.57 (2.74-11.21)		
Off-label because of indication asthma or indication COPD & asthma without ICS#																			

		THIN [UK] (N=7)			IPCI [NL] (N=1)			Aarhus [DK] (N=17)			HSD [IT] (N=1)			SIDIAP [ES] (N=167)			Pooled Data (N=202)		
<40 Years																			
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
				P> 15%			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**
	Yes	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	Nap	85 (54.14)	46.34-61.74	1.00000	92 (52.57)	45.2-59.83	1.00000
	No	Nap			Nap			Nap			Nap			72 (45.86)	38.26-53.66		83 (47.43)	40.17-54.8	
	Missing	Nap			Nap			Nap			Nap			19 (11.38)	7.41-17.09		27 (13.37)	9.35-18.75	

		THIN [UK] (N=1,151)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,728)			HSD [IT] (N=315)			SIDIAP [ES] (N=8,588)			Pooled Data (N=14,711)		
>=40 Years																			
Off-label categories	**Yes/No /Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
Off-label because of indication asthma#																			
	Yes	24 (2.14)	1.44-3.17	<0.0001	35 (3.77)	2.72-5.19	<0.0001	40 (1.72)	1.27-2.34	<0.0001	3 (1.36)	0.46-3.91	<0.0001	516 (6.4)	5.89-6.96	<0.0001	618 (4.88)	4.52-5.27	<0.0001
	No	1096 (97.86)	96.83-98.56		891 (95.91)	94.44-97.01		2281 (98.28)	97.66-98.73		218 (98.64)	96.09-99.54		7,549 (93.64)	93.08-94.15		12,035 (95.12)	94.73-95.48	

		THIN [UK] (N=1,151)			IPCI [NL] (N=930)			Aarhus [DK] (N=3,728)			HSD [IT] (N=315)			SIDIAP [ES] (N=8,588)			Pooled Data (N=14,711)		
>=40 Years																			
Off-label categories	**Yes/No/Unknown**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**	**N (%)**	**95% CI**	**P> 8%**
	Missing	31 (2.69)	1.9-3.8		3 (0.32)	0.11-0.95		1407 (37.74)	36.2-39.31		94 (29.84)	25.06-35.11		523 (6.09)	5.6-6.62		2058 (13.99)	13.44-14.56	
Duration of asthma Median - IQR		16.50 (4.77-20.63)			6.50 (2.01-10.65)			3.24 (0.48-11.49)			0.77 (0.07-0.77)			7.20 (2.26-11.08)			6.94 (2.19-11.28)		
Off-label because of indication asthma or indication COPD & asthma without ICS#																			
				P> 15%			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**			**P> 15%**
	Yes	78 (6.96)	5.62-8.61	<0.0001	61 (6.59)	5.16-8.37	<0.0001	54 (2.33)	1.79-3.02	<0.0001	4 (1.81)	0.71-4.56	<0.0001	620 (7.69)	7.13-8.29	<0.0001	817 (6.46)	6.04-6.9	<0.0001
	No	1042 (93.04)	91.39-94.38		865 (93.41)	91.63-94.84		2267 (97.67)	96.98-98.21		217 (98.19)	95.44-99.29		7445 (92.31)	91.71-92.87		11836 (93.54)	93.1-93.96	
	Missing	31 (2.69)	1.9-3.8		3 (0.32)	0.11-0.95		1407 (37.74)	36.2-39.31		94 (29.84)	25.06-35.11		523 (6.09)	5.6-6.62		2058 (13.99)	13.44-14.56	

missing excluded from denominator CI=Confidence interval

¥: proportion off-label use not provided as total number of patients < 20

Table 15-15 Description of disease codes registered at time of QVA149 prescription for patients where QVA149 is used for indications other than COPD, asthma, or COPD and asthma

Description	Numbers	Percentage
THIN (other indication) n= 54		
IDIOPATHIC PULMONARY FIBROSIS	1	1.85%
PLEURISY	1	1.85%
SPIROMETRY REVERSIBILITY	1	1.85%
WHEEZING	1	1.85%
BRONCHIECTASIS	2	3.70%
LUNGCANCER	3	5.56%
RESPIRATORY-NOT SPECIFIED	4	7.41%
COUGH	5	9.26%
DYSPNEA	6	11.11%
LRTI	8	14.81%
OTHER	22	40.74%
IPCI (other indication) n= 28		
ALLERGIC REACTION	1	3.57%
COUGH	1	3.57%
MILD OBSTRUCTIVE LUNGFUNCTION	1	3.57%
OBSTRUCTIVE AND RESTR SPIRO	1	3.57%

Description	Numbers	Percentage
PNEUMONIA	2	7.14%
RESTRICTIVE LUNGFUNCTION	2	7.14%
BRONCHITIS	3	10.71%
DYSPNEA	8	28.57%
LUNGCANCER	9	32.14%
AARHUS (other indication) n= 42		
PNEUMONITIS	1	2.38%
NASAL POLYP	1	2.38%
OTHER	1	2.38%
RESPIRATORY FAILURE	1	2.38%
ABSCESS OF LUNG	2	4.76%
PLEURAL EFFUSION	2	4.76%
OTHER RESPIRATORY DISORDERS	3	7.14%
ACUTE LOWER RESPIRATORY INFECT	3	7.14%
BRONCHIECTASIS	4	9.52%
UPPER RESPIRATORY TRACT DISEASES	4	9.52%
OTHER INTERSTITIAL PULMONARY D	6	14.29%
PNEUMONIA	14	33.33%
HSD (other indication) n=4		

Description	Numbers	Percentage
OTHER	1	25.00%
ACUTE BRONCHITIS	1	25.00%
SYMPTOMS INVOLVING RESPIRATORY SYSTEM AND OTHER CHEST SYMPTOMS	1	25.00%
ACUTE RESPIRATORY FAILURE	1	25.00%
SIDIAP (other indication) n=1,071		
Chronic rhinitis	1	0.09%
Other interstitial pulmonary diseases	1	0.09%
Chronic pharyngitis	1	0.09%
Hypertrophy of tonsils	1	0.09%
Hypertrophy of adenoids	1	0.09%
Other viral pneumonia	1	0.09%
Pneumothorax and air leak	1	0.09%
Acute bronchitis due to respiratory syncytial virus	1	0.09%
Influenza due to unidentified influenza virus	1	0.09%
Bacterial pneumonia, not elsewhere classified	1	0.09%
Pneumonia in diseases classified elsewhere	1	0.09%
Pneumonia, unspecified organism	1	0.09%
Unspecified respiratory condition due to chemicals,	1	0.09%

Description	Numbers	Percentage
gases, fumes and vapors		
Abnormal sputum	1	0.09%
Other specified symptoms and signs involving the circulatory and respiratory systems	1	0.09%
Pneumoconiosis due to other dust containing silica	1	0.09%
Allergic rhinitis due to pollen	1	0.09%
Unspecified pneumoconiosis	1	0.09%
Pneumonitis due to inhalation of food and vomit	1	0.09%
Other diseases of upper respiratory tract	1	0.09%
Pyothorax without fistula	1	0.09%
Mushroom-worker's lung	1	0.09%
Streptococcal tonsillitis	2	0.19%
Other respiratory disorders	2	0.19%
Acute recurrent sinusitis, unspecified	2	0.19%
Mouth breathing	2	0.19%
Other specified disorders of nose and nasal sinuses	2	0.19%
Chronic sinusitis	2	0.19%
Hiccough	2	0.19%
Acute tracheitis with obstruction	2	0.19%

Description	Numbers	Percentage
Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	3	0.28%
Pleural plaque	3	0.28%
Vasomotor and allergic rhinitis	3	0.28%
Unspecified bacterial pneumonia	3	0.28%
Acute laryngitis	3	0.28%
Pleurisy	4	0.37%
Lobar pneumonia, unspecified organism	4	0.37%
Vasomotor rhinitis	4	0.37%
Deviated nasal septum	4	0.37%
Pneumoconiosis due to asbestos and other mineral fibers	4	0.37%
Vasomotor and allergic rhinitis	4	0.37%
Chronic respiratory failure with hypoxia	5	0.47%
Respiratory failure, not elsewhere classified	6	0.56%
Acute upper respiratory infection, unspecified	6	0.56%
Interstitial pulmonary disease, unspecified	6	0.56%
Acute bronchiolitis, unspecified	7	0.65%
Pneumothorax, unspecified	8	0.75%
Pulmonary collapse	9	0.84%

Description	Numbers	Percentage
Acute recurrent tonsillitis, unspecified	9	0.84%
Bronchopneumonia, unspecified organism	10	0.93%
Influenza due to unidentified influenza virus with other respiratory manifestations	10	0.93%
Acute pharyngitis, unspecified	11	1.03%
Wheezing	13	1.21%
Pleural effusion, not elsewhere classified	15	1.40%
Acute bronchitis	18	1.68%
Other abnormalities of breathing	21	1.96%
Diseases of bronchus, not elsewhere classified	27	2.52%
Vasomotor and allergic rhinitis	27	2.52%
Other disorders of lung	29	2.71%
Other interstitial pulmonary diseases with fibrosis	31	2.89%
Pneumonia, unspecified organism	36	3.36%
Acute nasopharyngitis	64	5.98%
Bronchiectasis	98	9.15%
Unspecified acute lower respiratory infection	121	11.30%
Acute bronchitis, unspecified	132	12.32%
Cough	135	12.61%

Description	Numbers	Percentage
Orthopnea	140	13.07%

Table 15-16 History of comorbidities in patients initiating QVA149 (assessed at index date and considering the complete medical history of the patients) by database and pooled

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Cerebrovascular events:												
Stroke and TIA combined	100 (8.64)	7.15- 10.39	127 (13.66)	11.60- 16.01	310 (8.28)	7.44-9.20	40 (12.66)	9.44- 16.78	659 (7.52)	6.99-8.09	1,236 (8.29)	7.86-8.74
Stroke	77 (6.65)	5.35- 8.23	83 (8.92)	7.26- 10.93	230 (6.14)	5.42- 6.96	28 (8.86)	6.20- 12.51	469 (5.35)	4.90- 5.84	887 (5.95)	5.58- 6.34
TIA	57 (4.92)	3.82- 6.32	62 (6.67)	5.24- 8.45	106 (2.83)	2.35- 3.41	14 (4.43)	2.66- 7.30	221 (2.52)	2.21- 2.87	460 (3.08)	2.82- 3.37
Cardiovascular events:												
Ischemic heart disease:	230 (19.86)	17.67- 22.26	197 (21.18)	18.68- 23.92	823 (21.98)	20.68- 23.33	25 (7.91)	5.42- 11.42	724 (8.26)	7.70- 8.86	1,999 (13.40)	12.87- 13.96
Myocardial infarction	95 (8.20)	6.76- 9.93	103 (11.08)	9.22- 13.25	292 (7.80)	6.98- 8.70	15 (4.75)	2.90- 7.68	474 (5.41)	4.95- 5.90	979 (6.56)	6.18- 6.97
Angina Pectoris	206 (17.79)	15.69- 20.10	113 (12.15)	10.20- 14.41	735 (19.63)	18.39- 20.93	11 (3.48)	1.95- 6.12	307 (3.50)	3.14- 3.91	1,372 (9.20)	8.75- 9.67
Unstable angina pectoris	32 (2.76)	1.96- 3.88	23 (2.47)	1.65- 3.68	147 (3.93)	3.35- 4.60	1 (0.32)	0.06- 1.77	69 (0.79)	0.62- 1.00	272 (1.82)	1.62- 2.05
Unstable ischemic heart disease combined (MI and/or unstable AP)	113 (9.76)	8.18- 11.60	119 (12.80)	10.80- 15.10	366 (9.77)	8.86- 10.77	16 (5.06)	3.14- 8.07	526 (6.00)	5.52- 6.52	1,140 (7.64)	7.23- 8.08
Heart failure	121 (10.45)	8.82- 12.34	93 (10.00)	8.23- 12.10	352 (9.40)	8.51- 10.38	27 (8.54)	5.94- 12.15	668 (7.62)	7.08- 8.20	1,261 (8.46)	8.02- 8.91

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Severe cardiac arrhythmia:												
Atrial flutter/fibrillation	125 (10.79)	9.14- 12.71	103 (11.08)	9.22- 13.25	548 (14.63)	13.54- 15.80	36 (11.39)	8.34- 15.37	926 (10.57)	9.94- 11.23	1,738 (11.65)	11.15- 12.18
Ventricular tachycardia	0 (0.00)	0.00- 0.33	5 (0.54)	0.23- 1.25	16 (0.43)	0.26- 0.69	1 (0.32)	0.06- 1.77	15 (0.17)	0.10- 0.28	37 (0.25)	0.18- 0.34
Ventricular fibrillation	0 (0.00)	0.00- 0.33	5 (0.54)	0.23- 1.25	3 (0.08)	0.03- 0.24	0 (0.00)	0.00- 1.20	12 (0.14)	0.08- 0.24	20 (0.13)	0.09- 0.21
Torsade de Pointes/Long QT syndrome	0 (0.00)	0.00- 0.33	2 (0.22)	0.06- 0.78	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	2 (0.01)	0.00- 0.05
Severe cardiac arrhythmia combined	125 (10.79)	9.14- 12.71	110 (11.83)	9.91- 14.06	556 (14.85)	13.74- 16.02	37 (11.71)	8.62- 15.72	944 (10.77)	10.14- 11.44	1772 (11.88)	11.37- 12.41
Other cardiac arrhythmia												
Sick sinus syndrome	0 (0.00)	0.00- 0.33	1 (0.11)	0.02- 0.61	47 (1.26)	0.95- 1.66	3 (0.95)	0.32- 2.75	0 (0.00)	0.00- 0.04	51 (0.34)	0.26- 0.45
SVT	17 (1.47)	0.92- 2.34	12 (1.29)	0.74- 2.24	141 (3.77)	3.20- 4.42	2 (0.63)	0.17- 2.28	71 (0.81)	0.64- 1.02	243 (1.63)	1.44- 1.85
Premature depolarisation	11 (0.95)	0.53- 1.69	12 (1.29)	0.74- 2.24	44 (1.17)	0.88- 1.57	17 (5.38)	3.39- 8.45	97 (1.11)	0.91- 1.35	181 (1.21)	1.05- 1.40
AV block	2 (0.17)	0.05- 0.63	2 (0.22)	0.06- 0.78	64 (1.71)	1.34- 2.18	3 (0.95)	0.32- 2.75	169 (1.93)	1.66- 2.24	240 (1.61)	1.42- 1.82
Arterial hypertension	540 (46.63)	43.77- 49.51	390 (41.94)	38.80- 45.13	1,116 (29.80)	28.36- 31.28	185 (58.54)	53.04- 63.84	4,972 (56.73)	55.69- 57.77	7,203 (48.3)	47.50- 49.10

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Urinary retention or symptomatic bladder outflow obstruction	37 (3.20)	2.33- 4.37	12 (1.29)	0.74- 2.24	58 (1.55)	1.20- 2.00	3 (0.95)	0.32- 2.75	152 (1.73)	1.48- 2.03	262 (1.76)	1.56- 1.98
BPH#	59 (5.09)	3.97- 6.52	70 (7.53)	6.00- 9.40	238 (6.36)	5.62- 7.18	67 (21.20)	17.06- 26.04	1,853 (21.14)	20.30- 22.01	2,287 (15.34)	14.77- 15.92
Diabetes mellitus	212 (18.31)	16.19- 20.64	178 (19.14)	16.74- 21.79	354 (9.45)	8.56- 10.43	67 (21.20)	17.06- 26.04	2,155 (24.59)	23.70- 25.50	2,966 (19.89)	19.26- 20.54
Narrow-angle glaucoma	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	17 (0.45)	0.28- 0.73	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	17 (0.11)	0.07- 0.18
Other glaucoma	47 (4.06)	3.07- 5.36	33 (3.55)	2.54- 4.94	67 (1.79)	1.41- 2.27	26 (8.23)	5.68- 11.78	667 (7.61)	7.07- 8.18	840 (5.63)	5.27- 6.01
Liver disease	65 (5.61)	4.43- 7.09	26 (2.80)	1.91- 4.06	40 (1.07)	0.79- 1.45	20 (6.33)	4.13- 9.57	75 (0.86)	0.68- 1.07	226 (1.52)	1.33- 1.72
Chronic Kidney Disease												
Stage 1 (kidney damage with eGFR>= 90 mL/min/1.73m2)**	1 (0.09)	0.02- 0.49	0 (0)	0-0.41	0 (0)	0-0.1	29 (9.18)	6.47- 12.87	0 (0)	0-0.04	30 (0.20)	0.14- 0.29
Stage 2 (eGFR 60-89 mL/min/1.73m2)	574 (49.57)	46.69- 52.44	440 (47.31)	44.12- 50.53	1862 (49.72)	48.12- 51.32	133 (42.09)	36.77- 47.60	4,135 (47.18)	46.14- 48.23	7,144 (47.90)	47.10- 48.71
Stage 3 (eGFR 30-59 mL/min/1.73m2)	368 (31.78)	29.16- 34.52	128 (13.76)	11.70- 16.13	654 (17.46)	16.28- 18.71	82 (25.95)	21.43- 31.05	1,402 (16.00)	15.24- 16.78	2,634 (17.66)	17.06- 18.28

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Stage 4 (eGFR 15-29 mL/min/1.73m2)	39 (3.37)	2.47- 4.57	11 (1.18)	0.66- 2.11	70 (1.87)	1.48- 2.35	18 (5.70)	3.63- 8.82	117 (1.34)	1.12- 1.60	255 (1.71)	1.51- 1.93
Stage 5 (eGFR< 15 or dialysis)	4 (0.35)	0.13- 0.88	2 (0.22)	0.06- 0.78	4 (0.11)	0.04- 0.27	10 (3.16)	1.73- 5.73	19 (0.22)	0.14- 0.34	39 (0.26)	0.19- 0.36
Stage Unknown	7 (0.60)	0.29- 1.24	15 (1.61)	0.98- 2.64	25 (0.67)	0.45- 0.98	0 (0)	0-1.2	160 (1.83)	1.57- 2.13	207 (1.39)	1.21- 1.59
No CKD disease*	165 (14.25)	12.35- 16.38	334 (35.91)	32.89- 39.05	1,130 (30.17)	28.72- 31.66	44 (13.92)	10.54- 18.18	2,931 (33.44)	32.46- 34.44	4,604 (30.87)	30.14- 31.62

MI=Myocardial infarction; AP=Angina pectoris; TIA=Transient ischemic attack; CKD=Chronic kidney disease; SVT= Supraventricular tachycardia; AV=Atrioventricular; BPH=Benign prostatic hyperplasia # denominator males only, CKD=Chronic kidney disease; **CKD stage based on both disease codes and lab results. If CKD stage based on both disease codes and lab results were available, CKD stage closest and most severe to the index date is reported; **Stage 1 based on disease codes for CKD stage 1 only; *Defined as no event of CKD available AND no serum creatinine measurement OR this measurement results in a GFR ≥90 mL/min/1.73m^2

Table 15-17 History of comorbidities in patients initiating QVA149 (assessed at index date and considering the complete medical history of the patients) by calendar year

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Cerebrovascular events:										
Stroke and TIA combined	14 (11.29)	6.85-18.06	461 (7.96)	7.29- 8.68	696 (8.43)	7.85- 9.05	63 (8.57)	6.76-10.82	2 (22.22)	6.32-54.74
Stroke	12 (9.68)	5.62-16.16	322 (5.56)	5.00- 6.18	504 (6.11)	5.61- 6.64	48 (6.53)	4.96- 8.55	1 (11.11)	1.99-43.50
TIA	3 (2.42)	0.83- 6.87	169 (2.92)	2.51- 3.38	247 (2.99)	2.65- 3.38	40 (5.44)	4.02- 7.33	1 (11.11)	1.99-43.50

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Cardiovascular events:										
Ischemic heart disease:	31 (25.00)	18.21-33.29	793 (13.69)	12.83-14.60	1,033 (12.52)	11.82-13.25	142 (19.32)	16.63-22.33	0 (0.00)	0.00-29.92
Myocardial infarction	7 (5.65)	2.76-11.19	392 (6.77)	6.15- 7.44	517 (6.26)	5.76- 6.81	63 (8.57)	6.76-10.82	0 (0.00)	0.00-29.92
Angina Pectoris	23 (18.55)	12.69-26.30	546 (9.43)	8.70-10.21	677 (8.20)	7.63- 8.81	126 (17.14)	14.59-20.04	0 (0.00)	0.00-29.92
Unstable angina pectoris	6 (4.84)	2.24-10.16	104 (1.80)	1.48- 2.17	142 (1.72)	1.46- 2.02	20 (2.72)	1.77- 4.17	0 (0.00)	0.00-29.92
Unstable ischemic heart disease combined (MI and/or unstable AP)	13 (10.48)	6.23-17.11	445 (7.68)	7.02- 8.40	609 (7.38)	6.83- 7.96	73 (9.93)	7.97-12.31	0 (0.00)	0.00-29.92
Heart failure	14 (11.29)	6.85-18.06	475 (8.20)	7.52- 8.94	698 (8.46)	7.88- 9.08	72 (9.80)	7.85-12.16	2 (22.22)	6.32-54.74
Severe cardiac arrhythmia:										
Atrial flutter/fibrillation	22 (17.74)	12.02-25.40	682 (11.77)	10.97-12.63	944 (11.44)	10.77-12.14	88 (11.97)	9.82-14.52	2 (22.22)	6.32-54.74
Ventricular tachycardia	0 (0.00)	0.00- 3.00	21 (0.36)	0.24- 0.55	16 (0.19)	0.12- 0.31	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
Ventricular fibrillation	1 (0.81)	0.14- 4.43	9 (0.16)	0.08- 0.30	10 (0.12)	0.07- 0.22	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
Torsade de Pointes/Long QT syndrome	0 (0.00)	0.00- 3.00	1 (0.02)	0.00- 0.10	1 (0.01)	0.00- 0.07	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
Severe cardiac arrhythmia combined	23 (18.55)	12.69-26.30	702 (12.12)	11.30-12.99	957 (11.60)	10.92-12.30	88 (11.97)	9.82-14.52	2 (22.22)	6.32-54.74
Other cardiac arrhythmia										
Sick sinus syndrome	2 (1.61)	0.44- 5.69	31 (0.54)	0.38- 0.76	18 (0.22)	0.14- 0.34	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
SVT	6 (4.84)	2.24-10.16	100 (1.73)	1.42- 2.10	126 (1.53)	1.28- 1.81	11 (1.50)	0.84- 2.66	0 (0.00)	0.00-29.92

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Premature depolarisation	2 (1.61)	0.44- 5.69	67 (1.16)	0.91- 1.47	104 (1.26)	1.04- 1.52	8 (1.09)	0.55- 2.13	0 (0.00)	0.00-29.92
AV block	0 (0.00)	0.00- 3.00	103 (1.78)	1.47- 2.15	136 (1.65)	1.39- 1.95	1 (0.14)	0.02- 0.77	0 (0.00)	0.00-29.92
Arterial hypertension	41 (33.06)	25.40-41.74	2,680 (46.27)	44.99-47.56	4,119 (49.91)	48.83-50.99	359 (48.84)	45.25-52.45	4 (44.44)	18.88-73.34
Urinary retention or symptomatic bladder outflow obstruction	1 (0.81)	0.14- 4.43	84 (1.45)	1.17- 1.79	156 (1.89)	1.62- 2.21	21 (2.86)	1.88- 4.33	0 (0.00)	0.00-29.92
BPH#	9 (7.26)	3.87-13.22	880 (15.19)	14.29-16.14	1,355 (16.42)	15.63-17.23	42 (5.71)	4.26- 7.63	1 (11.11)	1.99-43.50
Diabetes mellitus	20 (16.13)	10.69-23.60	1099 (18.97)	17.99-20.00	1,703 (20.63)	19.78-21.52	142 (19.32)	16.63-22.33	2 (22.22)	6.32-54.74
Narrow-angle glaucoma	1 (0.81)	0.14- 4.43	10 (0.17)	0.09- 0.32	6 (0.07)	0.03- 0.16	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
Other glaucoma	3 (2.42)	0.83- 6.87	282 (4.87)	4.34- 5.45	526 (6.37)	5.87- 6.92	29 (3.95)	2.76- 5.61	0 (0.00)	0.00-29.92
Liver disease	4 (3.23)	1.26- 8.00	61 (1.05)	0.82- 1.35	126 (1.53)	1.28- 1.81	34 (4.63)	3.33- 6.39	1 (11.11)	1.99-43.50
Chronic Kidney Disease										
Stage 1 (kidney damage with eGFR>= 90 mL/min/1.73m2)**	0 (0)	0-3	1 (0.02)	0.00- 0.10	28 (0.34)	0.23- 0.49	1 (0.14)	0.02- 0.77	0 (0)	0-29.91
Stage 2 (eGFR 60-89 mL/min/1.73m2)	63 (50.81)	42.12-59.45	2758 (47.62)	46.33-48.90	3,951 (47.87)	46.80-48.95	368 (50.07)	46.46-53.67	4 (44.44)	18.88-73.34
Stage 3 (eGFR 30-59 mL/min/1.73m2)	21 (16.94)	11.35-24.51	925 (15.97)	15.05-16.94	1,444 (17.50)	16.69-18.33	240 (32.65)	29.36-36.13	4 (44.44)	18.88-73.34

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Comorbidities	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Stage 4 (eGFR 15-29 mL/min/1.73m2)	2 (1.61)	0.44- 5.69	79 (1.36)	1.10- 1.70	145 (1.76)	1.50- 2.06	28 (3.81)	2.65- 5.45	1 (11.11)	1.99-43.50
Stage 5 (eGFR< 15 or dialysis)	0 (0)	0-3	11 (0.19)	0.11- 0.34	25 (0.30)	0.21- 0.45	3 (0.41)	0.14- 1.19	0 (0)	0-29.91
Stage Unknown	1 (0.81)	0.14- 4.43	87 (1.50)	1.22- 1.85	114 (1.38)	1.15- 1.66	5 (0.68)	0.29- 1.58	0 (0)	0-29.91
No CKD disease*	207 (1.39)	1.21- 1.59	207 (1.39)	1.21- 1.59	207 (1.39)	1.21- 1.59	207 (1.39)	1.21- 1.59	207 (1.39)	1.21- 1.59

MI=Myocardial infarction; AP=Angina pectoris; TIA=Transient ischemic attack; CKD=Chronic kidney disease; SVT= Supraventricular tachycardia; AV=Atrioventricular; BPH=Benign prostatic hyperplasia # denominator males only, CKD=Chronic kidney disease; **CKD stage based on both disease codes and lab results. If CKD stage based on both disease codes and lab results were available, CKD stage closest and most severe to the index date is reported; **Stage 1 based on disease codes for CKD stage 1 only; *Defined as no event of CKD available AND no serum creatinine measurement OR this measurement results in a GFR ≥90 mL/min/1.73m^2

Table 15-18 Use of other respiratory drugs (assessed in the 6 months prior to the index date (including prescriptions on index date) by database and pooled

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Other respiratory drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Single ingredient LABA	250 (21.59)	19.32- 24.05	236 (25.38)	22.68- 28.27	1,268 (33.86)	32.36- 35.39	106 (33.54)	28.56- 38.92	2,134 (24.35)	23.46- 25.26	3,994 (26.78)	26.08- 27.50
Single ingredient LAMA	782 (67.53)	64.78- 70.17	453 (48.71)	45.51- 51.92	1,840 (49.13)	47.53- 50.73	132 (41.77)	36.47- 47.28	3,625 (41.36)	40.34- 42.40	6,832 (45.81)	45.01- 46.61
Single-ingredient short-acting muscarinic agents (SAMA)	31 (2.68)	1.89- 3.77	107 (11.51)	9.61- 13.72	20 (0.53)	0.35- 0.82	15 (4.75)	2.90- 7.68	2,180 (24.87)	23.98- 25.79	2,353 (15.78)	15.20- 16.37
Single-ingredient short-acting β_2-agonists (SABA)	1014 (87.56)	85.54- 89.34	359 (38.60)	35.53- 41.77	1,900 (50.73)	49.13- 52.33	45 (14.24)	10.82- 18.52	3,228 (36.83)	35.83- 37.85	6,546 (43.89)	43.10- 44.69
Inhaled corticosteroids (ICS)	111 (9.59)	8.02- 11.42	164 (17.63)	15.32- 20.22	735 (19.63)	18.39- 20.93	90 (28.48)	23.79- 33.69	2,279 (26.00)	25.10- 26.93	3,379 (22.66)	21.99- 23.34
Xanthines	48 (4.15)	3.14- 5.45	11 (1.18)	0.66- 2.11	24 (0.64)	0.43- 0.95	23 (7.28)	4.90- 10.68	175 (2.00)	1.72- 2.31	281 (1.88)	1.68- 2.12
LABA+ICS	353 (30.48)	27.90- 33.20	288 (30.97)	28.08- 34.01	1,150 (30.71)	29.25- 32.20	119 (37.66)	32.49- 43.12	2,680 (30.58)	29.62- 31.55	4,590 (30.78)	30.04- 31.52
SABA+ SAMA	2 (0.17)	0.05- 0.63	44 (4.73)	3.54- 6.29	137 (3.66)	3.10- 4.31	37 (11.71)	8.62- 15.72	41 (0.47)	0.35- 0.63	261 (1.75)	1.55- 1.97
Other												

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Other respiratory drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Oral ß$_2$-agonists	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	16 (0.43)	0.26- 0.69	0 (0.00)	0.00- 1.20	31 (0.35)	0.25- 0.50	47 (0.32)	0.24- 0.42
Leukotriene receptor antagonists (LTRA)	16 (1.38)	0.85- 2.23	16 (1.72)	1.06- 2.78	83 (2.22)	1.79- 2.74	8 (2.53)	1.29- 4.92	273 (3.12)	2.77- 3.50	396 (2.66)	2.41- 2.93
Systemic corticosteroids (overall)	443 (38.26)	35.50- 41.09	327 (35.16)	32.16- 38.29	1127 (30.09)	28.65- 31.58	102 (32.28)	27.36- 37.62	2357 (26.89)	25.98- 27.83	4356 (29.21)	28.49- 29.94
Systemic corticosteroids – indication COPD	155 (13.39)	11.54- 15.47	184 (19.78)	17.35- 22.47	418 (11.16)	10.19- 12.21	12 (3.80)	2.19- 6.52	322 (3.67)	3.30- 4.09	1,091 (7.32)	6.91- 7.74
Fixed combination LABA+LAMA	39 (3.37)	2.47- 4.57	5 (0.54)	0.23- 1.25	19 (0.51)	0.33- 0.79	1 (0.32)	0.06- 1.77	7 (0.08)	0.04- 0.16	71 (0.48)	0.38- 0.60
Oral phosphodiesterase 4 (PDE-4) inhibitors	0 (0.00)	0.00- 0.33	0 (0.00)	0.00- 0.41	9 (0.24)	0.13- 0.46	2 (0.63)	0.17- 2.28	144 (1.64)	1.40- 1.93	155 (1.04)	0.89- 1.22

SAMA= short acting muscarinic agents, SABA= short-acting β2-agonists, ICS= inhaled corticosteroids, LTRA=Leukotriene receptor antagonists, LABA= Long acting β2-agonists, LAMA= long acting muscarinic agents; PDE= Phosphodiesterase

Table 15-19 Use of other respiratory drugs (assessed in the 6 months prior to the index date (including prescriptions on index date) by calendar year

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Other respiratory drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Single ingredient LABA	56 (45.16)	36.68-53.93	1,917 (33.10)	31.90-34.32	1,892 (22.92)	22.03-23.84	127 (17.28)	14.72-20.18	2 (22.22)	6.32-54.74
Single ingredient LAMA	82 (66.13)	57.43-73.86	2,966 (51.21)	49.92-52.49	3,290 (39.86)	38.81-40.93	489 (66.53)	63.04-69.85	5 (55.56)	26.66-81.12
Single-ingredient short-acting muscarinic agents (SAMA)	8 (6.45)	3.31-12.22	876 (15.12)	14.22-16.07	1,455 (17.63)	16.82-18.47	14 (1.90)	1.14- 3.17	0 (0.00)	0.00-29.92
Single-ingredient short-acting β_2-agonists (SABA)	58 (46.77)	38.22-55.52	2,460 (42.47)	41.20-43.75	3389 (41.06)	40.01-42.13	632 (85.99)	83.29-88.31	7 (77.78)	45.26-93.68
Inhaled corticosteroids (ICS)	27 (21.77)	15.42-29.83	1,452 (25.07)	23.97-26.20	1,823 (22.09)	21.21-23.00	77 (10.48)	8.46-12.90	0 (0.00)	0.00-29.92
Xanthines	3 (2.42)	0.83- 6.87	90 (1.55)	1.27- 1.91	166 (2.01)	1.73- 2.34	22 (2.99)	1.98- 4.49	0 (0.00)	0.00-29.92
LABA+ICS	45 (36.29)	28.36-45.05	1,860 (32.11)	30.92-33.33	2,465 (29.87)	28.89-30.86	218 (29.66)	26.47-33.06	2 (22.22)	6.32-54.74
SABA+ SAMA	8 (6.45)	3.31-12.22	116 (2.00)	1.67- 2.40	136 (1.65)	1.39- 1.95	1 (0.14)	0.02- 0.77	0 (0.00)	0.00-29.92
Other										
Oral ß$_2$-agonists	1 (0.81)	0.14- 4.43	23 (0.40)	0.26- 0.60	23 (0.28)	0.19- 0.42	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
Leukotriene	5 (4.03)	1.73- 9.09	179 (3.09)	2.67- 3.57	201 (2.44)	2.12- 2.79	10 (1.36)	0.74- 2.49	1 (11.11)	1.99-43.50

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Other respiratory drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
receptor antagonists (LTRA)										
Systemic corticosteroids (overall)	43 (34.68)	26.87-43.40	1673 (28.88)	27.73-30.07	2346 (28.43)	27.46-29.41	291 (39.59)	36.12-43.17	3 (33.33)	12.06-64.58
Systemic corticosteroids – indication COPD	20 (16.13)	10.69-23.60	471 (8.13)	7.46- 8.86	511 (6.19)	5.69- 6.73	87 (11.84)	9.70-14.37	2 (22.22)	6.32-54.74
Fixed combination LABA+LAMA	0 (0.00)	0.00- 3.00	2 (0.03)	0.01- 0.13	38 (0.46)	0.34- 0.63	31 (4.22)	2.99- 5.92	0 (0.00)	0.00-29.92
Oral phosphodiesterase 4 (PDE-4) inhibitors	1 (0.81)	0.14- 4.43	90 (1.55)	1.27- 1.91	64 (0.78)	0.61- 0.99	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92

SAMA= short acting muscarinic agents, SABA= short-acting β2-agonists, ICS= inhaled corticosteroids, LTRA=Leukotriene receptor antagonists, LABA= Long acting β2-agonists, LAMA= long acting muscarinic agents; PDE= Phosphodiesterase

Table 15-20 Use of systemic anticholinergic drugs (assessed in the 6 months prior to the index date (including prescriptions on index date)) by database and pooled

	THIN [UK] (N=1,158)		IPCI [NL] (N=930)		Aarhus [DK] (N=3,745)		HSD [IT] (N=316)		SIDIAP [ES] (N=8,764)		Pooled Data (N=14,913)	
Systemic anticholinergic drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Antipsychotic drugs	72 (6.22)	4.97- 7.76	44 (4.73)	3.54- 6.29	210 (5.61)	4.92- 6.39	12 (3.80)	2.19- 6.52	409 (4.67)	4.24- 5.13	747 (5.01)	4.67- 5.37
Antidepressant agents (tricyclic and tetracyclic)	380 (32.82)	30.17- 35.57	152 (16.34)	14.11- 18.86	838 (22.38)	21.07- 23.74	48 (15.19)	11.65- 19.56	1,846 (21.06)	20.22- 21.93	3,264 (21.89)	21.23- 22.56
Disopyramide	0 (0.00)	0.00- 0.33	1 (0.11)	0.02- 0.61	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	1 (0.01)	0.00- 0.04
Antispasmodics	30 (2.59)	1.82- 3.67	16 (1.72)	1.06- 2.78	1 (0.03)	0.00- 0.15	1 (0.32)	0.06- 1.77	19 (0.22)	0.14- 0.34	67 (0.45)	0.35- 0.57
Antiparkinson drugs	2 (0.17)	0.05- 0.63	1 (0.11)	0.02- 0.61	7 (0.19)	0.09- 0.39	1 (0.32)	0.06- 1.77	17 (0.19)	0.12- 0.31	28 (0.19)	0.13- 0.27
Cholinesterase inhibitors	1 (0.09)	0.02- 0.49	1 (0.11)	0.02- 0.61	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	14 (0.16)	0.10- 0.27	16 (0.11)	0.07- 0.17
Atropine	0 (0.00)	0.00- 0.33	1 (0.11)	0.02- 0.61	0 (0.00)	0.00- 0.10	0 (0.00)	0.00- 1.20	0 (0.00)	0.00- 0.04	1 (0.01)	0.00- 0.04
H1 antihistaminics	138 (11.92)	10.18- 13.91	85 (9.14)	7.45- 11.16	181 (4.83)	4.19- 5.57	28 (8.86)	6.20- 12.51	1,270 (14.49)	13.77- 15.24	1,702 (11.41)	10.91- 11.93
Anticholinergics for treatment of overactive bladder	56 (4.84)	3.74- 6.23	22 (2.37)	1.57- 3.56	103 (2.75)	2.27- 3.32	1 (0.32)	0.06- 1.77	249 (2.84)	2.51- 3.21	431 (2.89)	2.63- 3.17

Table 15-21 Use of systemic anticholinergic drugs (assessed in the 6 months prior to the index date (including prescriptions on index date)) by calendar year

	2013 (N=124)		2014 (N=5,792)		2015 (N=8,253)		2016 (N=735)		2017 (N=9)	
Systemic anticholinergic drugs	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Antipsychotic drugs	6 (4.84)	2.24-10.16	279 (4.82)	4.29- 5.40	416 (5.04)	4.59- 5.53	45 (6.12)	4.61- 8.09	1 (11.11)	1.99-43.50
Antidepressant agents (tricyclic and tetracyclic)	28 (22.58)	16.11-30.70	1,247 (21.53)	20.49-22.61	1,751 (21.22)	20.35-22.11	235 (31.97)	28.70-35.43	3 (33.33)	12.06-64.58
Disopyramide	0 (0.00)	0.00- 3.00	7 (0.12)	0.06- 0.25	8 (0.10)	0.05- 0.19	1 (0.14)	0.02- 0.77	0 (0.00)	0.00-29.92
Antispasmodics	0 (0.00)	0.00- 3.00	15 (0.26)	0.16- 0.43	34 (0.41)	0.29- 0.58	18 (2.45)	1.55- 3.84	0 (0.00)	0.00-29.92
Antiparkinson drugs	0 (0.00)	0.00- 3.00	10 (0.17)	0.09- 0.32	17 (0.21)	0.13- 0.33	1 (0.14)	0.02- 0.77	0 (0.00)	0.00-29.92
Cholinesterase inhibitors	0 (0.00)	0.00- 3.00	7 (0.12)	0.06- 0.25	8 (0.10)	0.05- 0.19	1 (0.14)	0.02- 0.77	0 (0.00)	0.00-29.92
Atropine	0 (0.00)	0.00- 3.00	1 (0.02)	0.00- 0.10	0 (0.00)	0.00- 0.05	0 (0.00)	0.00- 0.52	0 (0.00)	0.00-29.92
H1 antihistaminics	8 (6.45)	3.31-12.22	630 (10.88)	10.10-11.71	978 (11.85)	11.17-12.57	86 (11.70)	9.57-14.23	0 (0.00)	0.00-29.92
Anticholinergics for treatment of overactive bladder	6 (4.84)	2.24-10.16	165 (2.85)	2.45- 3.31	231 (2.80)	2.46- 3.18	29 (3.95)	2.76- 5.61	0 (0.00)	0.00-29.92

Annex 2.2 - Comorbidity definition

Ischemic heart disease

Ischemic heart disease or myocardial ischemia, is a disease characterized by ischemia of the heart muscle, usually due to atherosclerosis of the coronary arteries.

For this study, ischemic heart disease as endpoint encompasses angina pectoris (both stable and unstable) and myocardial infarction.

Angina pectoris (eventtype=AP)(eventtype=UNSTABLEAP)

According to the guidelines of the European Heart Association; angina pectoris is described as chest discomfort due to myocardial ischaemia associated with coronary artery disease. Anginal symptoms are regarded as stable if they have been occurring over several weeks without major deterioration. They typically occur in conditions associated with increased myocardial oxygen consumption. Angina is said to be unstable if pre-existing angina worsens abruptly for no apparent reason or when new angina develops at a relatively low work load or at rest. (Fox et al 2006; Thygesen et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of angina pectoris.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33..	K74
Angina pectoris, unspecified	I20.9	413.9	G33z.	
Angina of effort	I20.8			
Anginal syndrome	I20.9			
Cardiac angina	I20.9			
Ischemic chest pain	I20.9		G33z400	
Ischaemic heart disease			G3...00	
			G3...13	
			G310.11	
			G31y.00	
			G34..00	
			G3y..00	
			G3z..00	
			Gyu3.00	
			Gyu3000	
Stenocardia			G33z1	
Unstable angina	I20.0		G311.00	K74.01
			G311.13	
			G311100	
			G330000	
Crescendo angina	I20.0		G311.11	
Intermediate coronary syndrome	I20.0	411.1		K76.01
Acute coronary syndrome				
			G311500	
			G33z000	
Angina at rest			G311.14	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			G311200	
Impending infarction			G311.12	
			G311000	
			G311011	
			G311z00	
			G312.00	
			G31y100	
			G31y200	
			G31y300	
			G31yz00	
Worsening angina			G311400	
Angina pectoris with documented spasm	I20.1		G31y000	
			G332.00	
Nocturnal angina			G330000	
Stable angina			G33z700	
Other forms of angina pectoris	I20.8		Gyu30	
Exercise induced angina			G33z300	
Refractory angina			G311300	
Frequency of angina			187..00	
H/O angina pectoris#			14A5.	
			14AJ.00	
Canadian Cardiovascular Society classification of angina			388E.00	
Cardiovascular Limitations and			388F.00	
Angina self-management plan agreed			661M000	
Angina self-management plan re			661N000	
Angina control			662K.00	
			662K000	
			662K100	
			662K200	
			662K300	
			662Kz00	
Antianginal therapy			8B27.00	
Coronary artery bypass graft operation planned			8L40.00	
Coronary angioplasty planned			8L41.00	
Other chronic ischaemic heart disease			G34..	

Not for acute event, will only be considered for angina pectoris as underlying comorbidity

Myocardial infarction (eventtype=MI)

Definition of Acute Myocardial Infarction (AMI)

Myocardial infarction is defined as necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation). Blockage of a coronary artery deprives the heart muscle of blood and oxygen, causing injury to the heart muscle Therefore, acute myocardial infarction is defined by the evidence of myocardial necrosis - in a clinical setting consistent with a) myocardial ischemia, including ST elevation b) myocardial infarction and c)

non-ST elevation myocardial infarction. In this study, an acute MI event will be ascertained using specific diagnoses codes for acute transmural myocardial infarction, acute subendocardial myocardial infarction, or unspecified acute myocardial infarction (Thygesen et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of myocardial infarction.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*			
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410.*	G30z.	K75
Acute myocardial infarction, unspecified	I21.9	410.9		
Myocardial infarction (acute) NOS	I21.3	410		
Acute myocardial infarction, unspecified site, episode of care unspecified		410.90		
AMI NOS, unspecified		410.90		
Acute myocardial infarction, sub endocardial infarction		410.7		
Old myocardial infarction#	I25.2	412	G32..00	
Healed myocardial infarction#			G32..11	
Subsequent/recurrent myocardial infarction	I22		G35..	
Subsequent myocardial infarction of unspecified site	I22.9		Gyu36	
Subsequent myocardial infarction of other sites	I22.8		Gyu35 G353.	
Subsequent myocardial infarction of anterior wall	I22.0		G350.	
Subsequent myocardial infarction of inferior wall	I22.1		G351.]	
Subsequent acute sub endocardial myocardial infarction	I22.2			
Subsequent non transmural myocardial infarction NOS	I22.2			
Subsequent myocardial infarction (acute) NOS	I22.9			
Re-infarction of myocardium			G35..	
Acute sub endocardial myocardial infarction	I21.4			
Acute myocardial infarction, sub endocardial infarction, episode of care unspecified		410.70		
Non transmural myocardial infarction	I21.4			
Acute myocardial infarction, of antero lateral wall		410.0	G300.	
Acute antero septal myocardial infarction			G3011	
Acute inferior myocardial infarction		410.4	G308.00	
Acute myocardial infarction, true posterior wall infarction		410.6		
True posterior myocardial infarction			G306.	
Acute myocardial infarction, of inferoposterior wall		410.3	G303.]	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Other specified anterior myocardial infarction			G301.]	
Acute transmural myocardial infarction of unspecified site	I21.3		Gyu34 G30X.00	
Acute transmural myocardial infarction of anterior wall	I21.0 122.0			
Acute transmural myocardial infarction of inferior wall	I21.1 I21.19 122.1			
Acute transmural myocardial infarction of other sites	I21.2 I21.29 122.8			
ECG: old myocardial infarction#			3232.	
Anterior myocard. infarct NOS		410.8	G301z	
Other acute myocardial infarct			G30y.	
Other acute myocardial inf.NOS			G30yz	
Inferior myocard. infarct NOS			G308.	
Acute myocardial infarction, of infero lateral wall		410.2	G302.	
Acute lateral myocardial infarction		410.5		
Lateral myocardial infarct NOS			G305.]	
Acute widespread myocardial infarction			X200S	
Acute posterior myocardial infarction		410.60 410.61 410.62		
Posterior myocard. infarct NOS			G304.]	
Silent myocardial infarct#			G30..17	
ECG: myocardial infarction			323..	
ECG: myocardial infarct NOS			323Z.	
Postoperative sub endocardial myocardial infarction			G384.00	
Postoperative myocardial infarction			G38z.00	
Acute anterior myocardial infarction		410.1		
Acute Q wave myocard infarct			G309.00	
Acute myocardial infarction, sub endocardial infarction		410.71 410.72		
Non-Q wave myocardial infarction NOS	I21.4 122.2			
Non-ST elevation (NSTEMI) myocardial infarction	I21.4 122.2			
History of MI#			14A3.00 14A4.00 14AH.00 14AT.00	K76.02
Diabetes mellitus insulin-glucose infuse acute myocardial infarct			889A.00	

Not for acute event, will only be considered for angina pectoris as underlying comorbidity

Heart failure (eventtype=HF)

Definition of heart failure

HF is a syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations. Patients with HF would usually be expected to show some improvement in symptoms and signs in response to those treatments from which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic or vasodilator administration) (Dickstein et al 2008).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for heart failure.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428.*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute heart failure			G582. G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure#			G5801	
H/O: heart failure#			14A6.00 14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01 402.91	G21z011	
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01 404.91		
Heart failure confirmed			1O1..00	
Heart failure management			661M500 661N500	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms				
Heart failure monitoring			662p.00 662T.00 662W.00 679W100	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			679X.00	
			67D4.00	
			8CL3.00	
			8CMK.00	
Cardiac failure therapy			8B29.00	
Heart failure follow-up			8HBE.00	
			8HHb.00	
			8HHz.00	
			8Hk0.00	
			8HTL.00	
Heart failure quality indicators			9hH..00	
			9hH0.00	
			9hH1.00	
Cardiomegaly			G5y3.00	
Post cardiac operation heart failure NOS			G5y4z00	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	
Heart failure as a complication of care			SP11111	

not for acute event, will only be considered for heart failure as underlying comorbidity

Stroke (eventtype=stroke)

Stroke is defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin: it includes patients presenting clinical signs and symptoms suggestive of intracerebral haemorrhage or cerebral ischemic necrosis. It does not include transient cerebral ischemia or stroke events in cases of blood disease (e.g. leukemia, polycythaemia vera), brain tumour or brain metastases. Secondary stroke caused by trauma should also be excluded.

In this study, a stroke event is defined as any form of stroke due to haemorrhage (intracerebral) or infarction (i.e. ischemic) and stroke not specified as haemorrhage or infarction. Potential cases of acute stroke will be ascertained by specific and unspecific diagnosis codes (Goldstein et al 2011).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of stroke.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64			
Stroke NOS	I63.9			K90
Non-traumatic subarachnoidal bleeding	I60	430	G60..	
Intracerebral haemorrhage	I61	431	G61..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Sequelae of stroke, not specified as hemorrhage or infarction#	I69	342	Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial haemorrhage	I62	432.*	G62..00 G62z.00	
Cerebral infarction	I63		G64..	
Personal history of stroke#			ZV125	
Sequelae of stroke NOS#	I69.3			
H/O: Stroke§			14A7.00 14A7.11 14A7.12 14AK.00	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000 G63y000	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits#	Z86.73	V12.54		
Management/monitoring of stroke			661M700 661N700 662e.00 662e.11 662M.00 662M100 662M200 662o.00 9Om..00 9Om0.00 9Om1.00 9Om2.00 9Om3.00 9Om4.00	
Delivery of rehabilitation for stroke			7P24200	
Stroke referral			8HBJ.00 8HTQ.00 8IEC.00	
Seen in stroke clinic			9N0p.00	
Quality indicators stroke			9h2..00 9h21.00 9h22.00	
Sequelae of cerebral infarction			G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction#		438.*	G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*	G6X..00/Gyu6G00	
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Discharge from stroke service			ZLEP.00	
Hemiplegia and hemiparesis		342.*		
Acute, but ill-defined, cerebrovascular disease		436.*		

not for acute event, will only be considered for stroke as underlying comorbidity

TIA (eventtype=TIA)

TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton et al 2009).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of TIA.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Transient cerebral ischemic attack, unspecified	G45.9			
TIA - Transient ischemic attack	G45	435.*	G65..12	K89
H/O: TIA			14AB.00	
			ZV12D00	
Amaurosis fugax			F423600	
Retinal transient arterial occlusion NOS			F423700	
Other transient cerebral ischemic attacks and related syndromes	G45.8		Fyu55	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits#		V12.54		
Transient ischaemic attack clinical management plan			8CRB.00	
Transient cerebral ischaemia			G65..00	
Drop attack			G65..11	
Other transient cerebral ischaemia			G65y.00	
Transient cerebral ischaemia NOS			G65z.00	
Impending cerebral ischaemia			G65z000	
Intermittent cerebral ischaemia			G65z100	
Transient cerebral ischaemia NOS			G65zz00	

not for acute event, will only be considered for stroke as underlying comorbidity

Cardiac arrhythmia

Atrial flutter (AFL) (eventtype=AFIFLUT) is an abnormal heart rhythm that occurs in the atria of the heart. When it first occurs, it is usually associated with a fast heart rate or tachycardia (beats over 100 per minute). On ECG, AFL is defined as presence of flutter waves (Camm et al 2010).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial flutter.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial flutter		427.32	G5731	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
Type I atrial flutter	I48.3			
Type II atrial flutter	I48.4			
Atypical atrial flutter	I48.4			
Unspecified atrial flutter	I48.92			
ECG: atrial flutter			3273.00	
History of atrial flutter#			14AR.00	

Not for acute event, will only be considered for atrial flutter as underlying comorbidity

Atrial fibrillation (AF) (eventtype=AFIFLUT) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. It is often associated with palpitations, fainting, chest pain, or congestive heart failure. By definition, the heart rate will be greater than 100 beats per minute. According to the ESC guidelines, the ECG shows absence of P waves, with disorganized electrical activity in their place, and irregular R-R intervals due to irregular conduction of impulses to the ventricles (Camm et al 2010)

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial fibrillation.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial fibrillation		427.31	G5730	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
AF - Paroxysmal atrial fibrillation			G573200	K79.01
Chronic atrial fibrillation#	I48.2			
Persistent atrial fibrillation	I48.1		G573500	
Permanent atrial fibrillation	I48.2		G573400	
Non-rheumatic atrial fibrillation			G573300	
ECG: atrial fibrillation			3272.	
H/O: atrial fibrillation#			14AN.00	
Atrial fibrillation resolved#			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	
			8HTy.00	
			9hF1.00	
			9Os..	

Not for acute event, will only be considered for atrial fibrillation as underlying comorbidity

Ventricular tachycardia (*eventtype*=***VENTTACH***) is a rapid heartbeat that originates in one of the ventricles of the heart. To be classified as tachycardia, the heart rate is usually at least 100 beats per minute (Zipes et al 2006).

Ventricular fibrillation (*eventtype=**VENTFIBR***) is a very rapid, uncoordinated, ineffective series of contractions throughout the ventricles of the heart. Unless stopped, these chaotic impulses are fatal (Zipes et al 2006).

Torsade de pointes *(eventtype=**TORSPOINT**)* is an uncommon and distinctive form of polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. Torsade de pointes, is associated with a prolonged QT interval, which may be congenital or acquired. Torsade usually terminates spontaneously but frequently recurs and may degenerate into ventricular fibrillation (Zipes et al 2006).

The following concepts of **ventricular arrhythmia** (ventricular tachycardia, ventricular fibrillation and Torsade de pointes) have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Ventricular tachycardia	I47.2		G571.11	K79.02
Paroxysmal ventricular tachycardia		427.1	G571.00	
ECG: ventricular tachycardia			3282.	
Ventricular fibrillation and flutter	I49.0	427.4	G574.	
ECG: ventricular fibrillation			3282.00	

Long QT syndrome (LQTS) (eventtype = LONGQT) is a congenital disorder characterized by a prolongation of the QT interval on electrocardiograms (ECGs) and a propensity to ventricular tachyarrhythmias, such as Torsade de Pointes, which may lead to syncope, cardiac arrest, or sudden death.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of long QT syndrome.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Long QT syndrome	I45.81 147.2E	426.82	X202	
ECG: Q-T interval prolonged			32K3.00	

Supraventricular tachycardia (SVT) (eventtype =SVT) is a condition presenting as a rapid heart rhythm originating at or above the atrioventricular node. Supraventricular tachycardias can be contrasted with the potentially more dangerous ventricular tachycardias—rapid rhythms that originate within the ventricular tissue.

Although "SVT" can be due to any supraventricular cause, the term is most often used to refer to a specific example, paroxysmal supraventricular tachycardia (PSVT), two common types being atrioventricular reciprocating tachycardia and AV nodal reentrant tachycardia.

The following concepts of sinus tachycardia have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
supraventricular tachycardia	I47.1			K79.01

Terms	ICD10	ICD9CM	Read Codes	ICPC
paroxysmal supraventricular tachycardia		427.0		
paroxysmal tachycardia	147			K79
paroxysmal tachycardia, unspecified	147.9			
re-entry ventricular arrhythmia	147.0			
Wolf Parkinson White syndrome	145.6			
History of supraventricular tachycardia[#]			14AQ.00	
ECG: supraventricular arrhythmia			327..00	
Paroxysmal supraventricular tachycardia			G570.00	
ECG: paroxysmal atrial tachy.			3274.00	
ECG: supraventric. arryth. NOS			327Z.00	
Wolff-Parkinson-White syndrome			G567400	
Paroxysmal atrial tachycardia			G570000	
Paroxysmal atrioventricular tachycardia			G570100	
Paroxysmal atrioventricular tachycardia			G570100	
Paroxysmal junctional tachycardia			G570200	
Paroxysmal nodal tachycardia			G570300	
Paroxysmal supraventricular tachycardia NOS			G570z00	
Supraventricular tachycardia NOS			G57y900	
Re-entry ventricular arrhythmia			G57yA00	

[#] Not for acute event, will only be considered for SVT as underlying comorbidity

Sick Sinus Syndrome (eventtype=SICKSINUS) is characterized by dysfunction of the sinoatrial (SA) node that is often secondary to senescence of the SA node and surrounding atrial myocardium. It is characterized by chronic SA node dysfunction, a sluggish or absent SA nodal pacemaker after electrical electroversion, frequently depressed escape pacemakers, and/or atrioventricular (AV) nodal conduction disturbances. These abnormalities can result in profound sinus bradycardia, sinus pauses, sinus arrest, SA nodal exit block, and inappropriate responses to physiological demands during exercise or stress.

The following concepts of Sick Sinus Syndrome have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Sick sinus syndrome	149.5 I47.2E		G57y300	K79.02

Atrioventricular (AV) block (eventtype=AVBLOCK) is a partial or complete interruption of impulse transmission from the atria to the ventricles. The most common cause is idiopathic fibrosis and sclerosis of the conduction system. Diagnosis is by ECG; symptoms and treatment depend on degree of block (first, second or third degree AV block), but treatment, when necessary, usually involves pacing.

The following concepts of atrioventricular block have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read codes	ICPC
Atrioventricular block, first degree	I44.0	426.11	G561311	
Atrioventricular block, complete	I44.2	426.0	G560.	
Third degree atrioventricular block			G560.	

Terms	ICD10	ICD9CM	Read codes	ICPC
Atrioventricular block, second degree	I44.1		G561400	
Other and unspecified atrioventricular block	I44.3	426.1	Gyu5U	
Unspecified atrioventricular block	I44.3	426.10	G561z	K84.02
			G5610	
Atrioventricular and left bundle-branch block	I44			
Mobitz (type) II atrioventricular block		426.12	G5612	
Other second degree atrioventricular block		426.13		
ECG: complete atrioventricular block			3298.	
Partial atrioventricular block			G561.	
ECG: partial atrioventricular block			3294.	
ECG: partial atrioventricular block - 2:1			3295.	
ECG: partial atrioventricular block - 3:1			3296.	
ECG: heart block			329..00	

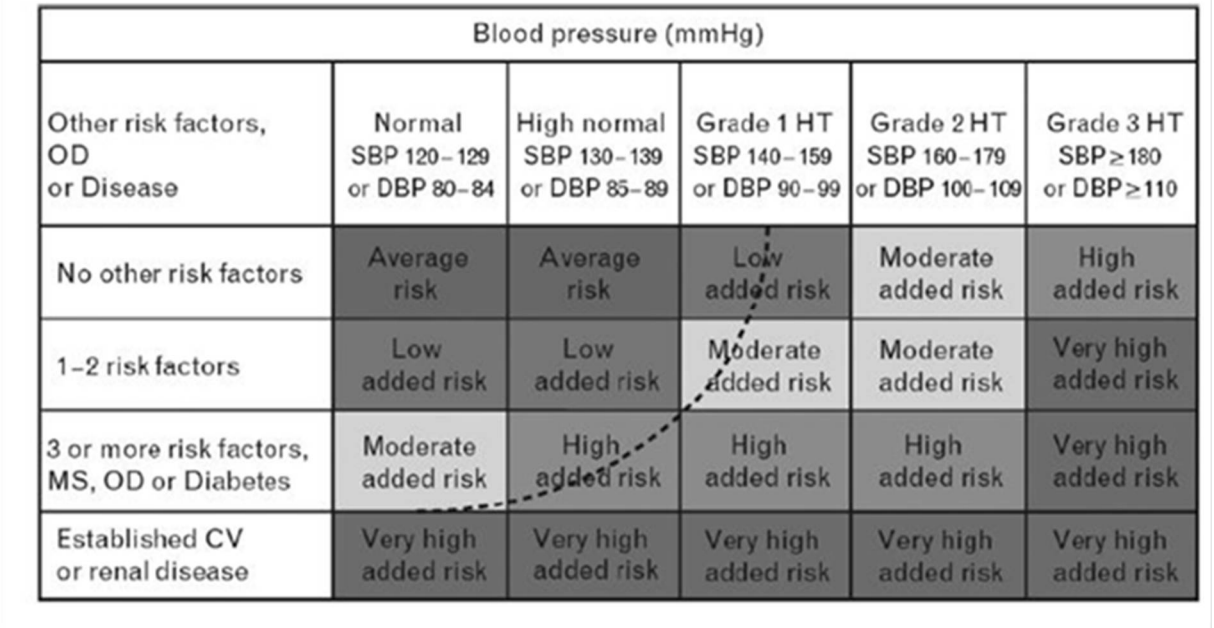
Premature depolarization (eventtype=PREMATDEP) will include atrial premature depolarization, junctional premature depolarization and ventricular premature depolarization.

The following concepts of premature depolarization have been mapped through the Unified Medical Language System (UMLS).

Terms	ICD10	ICD9CM	Read codes	ICPC
Extrasystole	I49.4	427.6	G576z00	K80
	I49.40		G576011	
	I49.49			
Supraventricular extrasystole		427.61	G576100	K80.01
Ventricular extrasystole	I49.3		G576500	K80.02
			G576200	
Atrial premature depolarization	I49.1		G576300	
Junctional premature depolarization	I49.2		G576400	
[X]Other and unspecified premature depolarization			Gyu5Z00	
ECG: ectopic beats		427.6	326..00	
ECG: extrasystole			3262.00	
ECG: ventricular ectopics			3263.00	
ECG: atrial ectopics			3264.00	
ECG: ectopic beats NOS			326Z.00	
Ectopic beats			G576.00	
Premature beats			G576.11	
Ectopic beats unspecified			G576000	

Definition of arterial hypertension (eventtype=AHT)

According to the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension, a patient is defined as having hypertension when the systolic blood pressure is above 140 mm Hg and the diastolic blood pressure is above 90 mm Hg. [ESH/ESC 2007].



Blood pressure (mmHg)					
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for arterial hypertension.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive diseases	I10-I15.9	401-405.99	Gyu2. G2...*	
high blood pressure	I10			
High blood pressure disorder				
Uncomplicated hypertension				K86
Hypertension with involvement target organs				K87
Renovascular hypertension	I15.0			
Secondary hypertension	I15	405	G24..	
Secondary hypertension, unspecified	I15.9		G24z.	
Malignant essential hypertension		401.0	G200.	
Essential (primary) hypertension	I10	401		
Hypertension NOS		401.9		
Benign hypertension		401.1	G201.	
Other secondary hypertension	I15.8	405.99	Gyu20	
Malignant secondary hypertension		405.0	G240.	
		405.09	G240z	
Benign secondary hypertension		405.1	G241	
		405.19	G241z	
Malignant hypertension			Xa3fQ G200.00	
Hypertension monitoring			662..*	

Definition of asthma (eventtype=ASTHMA)

According to the GINA (Global Initiative for Asthma) guidelines, asthma is a disorder defined by its clinical, physiological and pathological characteristics. The predominant feature of the

clinical history is episodic shortness of breath, particularly at night often accompanied by cough (Bateman et al 2008).

The following concepts of disease have been mapped through the UMLS for the outcomes of asthma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493.*	H33..	R96
Asthma, unspecified	J45.9	493.90	H33z	
Nonallergic asthma	J45.1	493.1	H331z	
Intrinsic asthma			H331z	
Mixed asthma	J45.8		H332.	
Atopic asthma	J45			
extrinsic allergic asthma	J45	493.0	H330z	
Predominantly allergic asthma	J45.0			
Confirmed asthma			1O2..00	
Extrinsic asthma with asthma attack		493.02	663d.00	
			663m.00	
Intrinsic asthma + attack		493.12		
Number of asthma exacerbations in past year			663y.00	
Emergency admission, asthma			8H2P.00	
Status asthmaticus	J46	493.91		
Extrinsic asthma with status asthmaticus		493.01		
Intrinsic asthma NOS		493.10		
Intrinsic asthma with status asthmaticus		493.11		
chronic obstructive asthma		493.2		
Other forms of asthma		493.8		
Asthma severity			663V.00	
Mild asthma			663V100	
Moderate asthma			663V200	
Severe asthma			663V300	
History of asthma			14B4.00	
Asthma quality indicators			9hA..00	
			9hA1.00	
			9hA2.00	

Definition of chronic kidney disease (eventtype=CKD)

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate <60 mL/min/1.73 m2 for at least 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (Levey and Coresh 2012).

The different stages of chronic kidney disease are described in the table below:

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29

Stage	Description	GFR (mL/min/1.73 m^2)
5	Kidney failure	< 15 or dialysis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of chronic kidney disease.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic kidney disease	N18	585.9	1Z1..	U99
	N18.9	583*	K05..13	
		585*		
		586*		
Hypertensive chronic kidney disease	I12	403		
Chronic kidney disease, Stage I		585.1	1Z10.00	
			1Z17.00	
			1Z18.00	
			1Z18.11	
			K051.00	
End stage renal disease		585.6	K050.00	
			K0D..00	
Chronic kidney disease, Stage 5		585.5	1Z14.00	
			1Z1K.00	
			1Z1K.11	
			1Z1L.00	
			1Z1L.11	
			K055.00	
Hypertensive chronic kidney disease, malignant		403.0		
Hypertensive heart and chronic kidney disease	I13	404		
Chronic kidney disease, stage 2 (mild)	N18.2	585.2	1Z11.00	
			1Z19.00	
			1Z19.11	
			1Z1A.00	
			1Z1A.11	
			K052.00	
Chronic kidney disease, stage 3 (moderate)	N18.3	585.3	1Z12.00	
			1Z15.00	
			1Z16.00	
			1Z1B.00	
			1Z1B.11	
			1Z1C.00	
			1Z1C.11	
			1Z1D.00	
			1Z1D.11	
			1Z1E.00	
			1Z1E.11	
			1Z1F.00	
			1Z1F.11	
			1Z1G.00	
			1Z1G.11	
			K053.00	
Chronic kidney disease, stage 4 (severe)	N18.4	585.4	1Z13.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			1Z1H.00	
			1Z1H.11	
			1Z1J.00	
			1Z1J.11	
			K054.00	
Hypertensive heart and chronic kidney disease, malignant		404.0		
		403.xx, 404.xx		
Renal failure	N17-N19.9	586	D215.00	
			D215000	
			K05..00	
			K05..12	
			K050.00	
			K06..00	
			K06..12	
Other chronic renal failure	N18.8		Kyu21	
Chronic kidney diseases monitoring/self-management			661M200	
			661N200	
			66i..00	
			6AA..00	
			9Ni9.00	
			9Ot..00	
			9Ot0.00	
			9Ot1.00	
			9Ot2.00	
			9Ot3.00	
			9Ot4.00	
Dialysis		V45.1	7L1..	
		V56.0	SP06B00	
		V56.8	Z1A..	
			Z91A.00	
			Z91A100	
			ZV45100	
			ZV56..	
			ZVu3G00	
CKD quality indicators			9hE..00	
			9hE0.00	
			9hE1.00	
Predicted stage chronic kidney			9Ot5.00	
Renal impairment			K060.00	
Impaired renal function			K060.11	
Acute-on-chronic renal failure			K0E..00	
Kidney transplantation		V42.0, 996.81	SP08300	
		250.4x	SP08C00	
			SP08D00	
			SP08E00	
			SP08F00	
			SP08G00	
			SP08H00	

If available, kidney function will be derived from the lab results (calculation of glomerular filtration rate = creatinine clearance) using the following formula:

GFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 (Levey et al 2009).

Based on the actual value of the GFR, it will be possible to describe the stage of chronic kidney disease. In addition, code specific terms by stage (see above) will be used.

Definition of hepatic impairment (eventtype=HEPAR)

Hepatic function decreases with age, but due to the high capacity of the liver this is considered not to change the pharmacokinetics to a clinically relevant extent. Liver disease, however, is known to be a common cause of altered pharmacokinetics of drugs. Hepatic function can be decreased through different pathophysiological mechanisms. Worldwide, chronic infections with hepatitis B or C are the most common causes of chronic liver disease, whereas in the western world, chronic and excessive alcohol ingestion is one of the major causes of liver disease. Other causes are uncommon diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune chronic active hepatitis. Ongoing destruction of the liver parenchyma in chronic liver diseases ultimately leads to liver cirrhosis and the development of portal hypertension. However, even if liver cirrhosis is established, the residual metabolic function of the liver may be rather well preserved for many years because of regeneration of hepatocytes. Clinical symptoms related to hepato-cellular failure and portal hypertensions are most importantly ascites, oesophageal varices and encephalopathy. Serum markers of liver failure are low serum albumin and a prothrombin deficiency. Serum bilirubin as well as other liver tests may or may not be affected to a varying degree, e.g. depending on the liver disease (cholestatic versus hepatocellular). Liver cirrhosis is irreversible in nature, but progression can be modified by e.g. abstinence of alcohol in alcohol liver cirrhosis (EMA 2005).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Liver enzymes abnormal	R94.5 R74	794.8	44G2. R148. 44D2. 44G3100 44G4100 44H5100 44H5200 R148.00	
Hepatic failure, unspecified	K72.9			

Terms	ICD10	ICD9CM	Read Codes	ICPC
Liver failure			7L1f.00	
			7L1fy00	
			7L1fz00	
			J625.00	
			J625.11	
			J62y.11	
			J62y.12	
			J62y.13	
Cirrhosis; liver	K74.60	571.5	J615..	D97
Hepatic failure, unspecified				
Nonspecific elevation of levels of transaminase or LDH		790.4		
Inflammatory liver disease, unspecified	K75.9			
Hepatitis NOS		573.3	J633.	
Hepatitis unspecified				
Unspecified viral hepatitis	B19	070	A70z.	D72
Viral hepatitis	B19.9		A70..	
			A72x000	
			A785200	
			AyuB..	
			J63..	
Chronic hepatitis, unspecified	K73.9	571.4	J614..	
			J614y	
Alcoholic cirrhosis or fibrosis	K70.2			
	K70.3			
	K70.4			
Primary or secondary biliary cirrhosis	K74.3			
	K74.4			
	K74.5			
History of hepatitis			141E.00	
			141F.00	
			2126700	
H/O: liver disease			14C5.00	
Hepatitis A - current infection			2J23.00	
Chronic hepatitis			9kR..00	
			9kR..11	
Hepatitis screening positive			9kV..00	
			9kV..11	
			9kZ..00	
			9kZ..11	
Sequelae of viral hepatitis			AE23.00	
			AyuJ900	
Acute liver failure			J600011	
Acute hepatitis - noninfective			J600100	
Necrosis of liver			J600z00	
			J601.00	
Cirrhosis and chronic liver disease			J61..	
Other sequelae of chronic liver			J62y.00	
[X]Diseases of the liver			Jyu7..	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Liver transplant failure and rejection			SP08600	
Liver failure as a complication of care			SP14211	

Definition of LRTI (indication of use of antibiotics)

Definition of lower respiratory tract infection (eventname=LRTI)

Lower respiratory tract infection consists of both pneumonia and (acute) bronchitis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for lower respiratory tract infection.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Pneumonia, (unspecified)	J18*		X100E	R81
			H2*	
Bacterial pneumonia, (unspecified)	J15.9	482.9	X100H	
			H22z.	
Atypical pneumonia	J16.8		H28.00	
Viral pneumonia	J12.9	480	XE0YG	
	J10.0	480.9	H2*.	
Acute bronchitis	J20	466	H06..	R78
Acute tracheo-bronchitis	J20.9	466.0	XE0Xr	
			H060z	
			H0605	

Glaucoma (narrow angle glaucoma and other) (eventtype =GLAUCOME)

Definition of narrow angle glaucoma

Narrow angle glaucoma, also called acute angle closure glaucoma or closed angle glaucoma, is a rare type of glaucoma in which symptoms usually come on suddenly. Unlike most glaucoma, people with narrow angle glaucoma usually have severe symptoms including pain, blurry vision, redness and nausea. Some people also complain of seeing halos around lights.

Narrow angle glaucoma is caused by an acute blockage of the drainage canal where fluid normally flows freely out of the eye. A buildup of fluid causes a sudden increase in intraocular pressure.

Narrow angle glaucoma requires a quick diagnosis and rapid treatment, as significantly decreased vision or blindness can result within hours (Casson et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of narrow angle glaucoma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Anatomical narrow angle borderline glaucoma		365.02	F450200	
Acute angle-closure glaucoma	H40.21	365.22	F452	F93.02
Primary angle-closure glaucoma	H40.2		F452.00	
Closed angle glaucoma			F452.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Primary angle-closure glaucoma			F452..	
Glaucoma due to chamber angle anomaly			F454000	

Definitions of other glaucoma

Open-angle glaucoma, the most common form of glaucoma, accounting for at least 90% of all glaucoma cases: It is caused by the slow clogging of the drainage canals, resulting in increased eye pressure. In contrast to narrow angle glaucoma, it has as wide and open angle between the iris and cornea. Open angle glaucoma develops slowly and is a lifelong condition and often has symptoms and eye damage that are not immediately noticed.

In normal tension glaucoma, the optic nerve is damaged even though the eye pressure is not very high.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of glaucoma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
glaucoma	H40-H42.9	365	F45	F93
Glaucoma - absolute			F404211	
Glaucomatocyclitic crises			F442100	
[X]Glaucoma			FyuG.00	

Bladder obstruction/urinary retention/BPH

Definition of bladder obstruction/urinary retention *(eventtype=URINRETENTION)*

Urinary retention describes a bladder that does not empty completely or does not empty at all. Historically, urinary retention has been classified as either acute or chronic the latter is generally classified as high pressure or low pressure according to the bladder filling pressure on urodynamic ([redacted]).

Bladder outlet obstruction (BOO) is a blockage at the base of the bladder that reduces or prevents the flow of urine into the urethra, the tube that carries urine out of the body. Bladder outlet obstruction (BOO) can have many different causes, including benign prostatic hyperplasia (BPH), bladder stones, bladder tumors (cancer), pelvic tumors (cervix, prostate, uterus, rectum) and urethral stricture (scar tissue)

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of urinary retention.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Urinary Retention	R33	788.2 788.20	R082..	U05.02
Cannot pass urine – retention			1A32.00	
Acute retention of urine			R0822	
Retention symptoms			1A32.11	
Micturition stream poor			1A33.00	
Hesitancy			1A34.00	
Hesitancy of micturition			1A34.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
BOO - Bladder outflow obstruction			K160.13	
Bladder outflow obstruction			K165200	
Bladder neck obstruction	N32.0	596.0		

Definition of BPH *(eventtype=BPH)*

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The enlarged gland has been proposed to contribute to the overall lower urinary tract symptoms (LUTS) complex via at least two routes: (1) direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and (2) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to the physical presence of BOO. Detrusor overactivity is thought to be a contributor to the storage symptoms seen in LUTS. (Juliao et al 2012)

Terms	ICD10	ICD9CM	Read Codes	ICPC
16 Benign prostatic hypertrophy/ Benign prostatic hyperplasia	N40	600.0	K20*	Y85
Prostatic hyperplasia			K20z. K200.	
Benign neoplasm of prostate			B7C2.00	

Pregnancy and breast feeding (eventtype=PREGNANCY, eventtype=BREASTFEED)

Information on breast feeding and pregnancy will be retrieved from IPCI, HSD and THIN via specific ICPC or READ codes. Information on pregnancy in Aarhus is derived via linkage with the birth register

Terms	ICD10	Read Codes	ICPC
Pregnancy	Z32.1 030*		
Serum pregnancy test positive		4453.00	
Urine pregnancy test positive		4654.00	
Pregnancy associated plasma protein A level		4Q3N.00	
Pregnancy associated plasma protein A multiple of median		4Q3N000	
IUD failure – pregnant		615C.00	
Pregnant, IUD failure		615C.11	
Pregnant, diaphragm failure		6166.00	
Pregnant, sheath failure		6174.00	
Pregnant		62... ZV..	W78 W79

Terms	ICD10	Read Codes	ICPC
Pregnancy advice		67A..00	
Curettage of term pregnancy NE		7E07111	
Suction termination of pregnancy		7E08400	
Vacuum termination of pregnancy		7E08411	
Termination of pregnancy NEC		7E08600	W83
Pregnancy operations		7F...12	
Pregnancy prophylactic therapy		8B68.00	
		8B7..11	
		8B74.00	
		8B75.00	
Complications of pregnancy, childbirth and the puerperium		L....00	W03
		Ly...00	W05
		Lz...00	W17
			W18
			W28
			W29
			W70
			W71
			W72
			W73
			W75
			W76
			W77
			W80
			W81
Termination of pregnancy		L05..12	W82
		L095.00	
		L097.00	
Other specified pregnancy with abortive outcome		L0y..00	
		L0z..00	
Pregnancy complications		L1...	
Risk factors in pregnancy		L2...	W84
Caesarean section – pregnancy		L398200	
Venous complications during pregnancy		L41..	W77
Nipple complications during pregnancy		L46..	
Pregnancy, childbirth and puerperium observations		Z2...	W91
			W92
			W93
			W96
			W99
Lactation established		62PD.00	
Obstetric breast and lactation		L46..	W19
			W20
Lactation management		Z2B5.00	W94
			W94

Terms	ICD10	Read Codes	ICPC
			W95
Establishing lactation		Z2B5400	
Promotion of lactation		Z2B5412	
Dietary advice for lactation		ZC2L.11	

Annex 2.3 – Exposure definition – respiratory medication use

QVA149

	ATC code
QVA149	R03AL04

Concomitant use of other respiratory medications

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
SAMA	R03BB01	Ipratropium bromide	x	x	x	x	x
	R03BB02	Oxitropium bromide	x	no	no	x	no
LAMA	R03BB04	Tiotropium bromide	x	x	x	x	x
	R03BB05	Aclidinium bromide	x	x	no	x	x
	R03BB06	Glycopyrronium bromide	x	x	x	x	x
	R03BB07	Umeclidinium bromide	x	no			
SABA	R03AC02	Salbutamol	x	x	x	x	x
	R03AC03	Terbutaline	x	x	x	x	x
	R03AC04	Fenoterol	x	no	x	x	no
	R03AC05	Rimiterol	x	no	no	no	no
	R03AC06	Hexoprenaline	no	no	no	no	no
	R03AC07	Isoetarine	no	no	no	no	no
	R03AC08	Pirbuterol	x	no	no	no	no
	R03AC09	Tretoquinol	no	no	no	no	no
	R03AC10	Carbuterol	no	no	no	no	no
	R03AC15	Reproterol	x	no	no	no	no
	R03AC16	Procaterol	no	no	no	no	no
	R03AC17	Bitolterol	no	no	no	no	no
LABA	R03AC11	Tulobuterol	no	no	no	no	no
	R03AC12	Salmeterol	x	x	x	x	x
	R03AC13	Formoterol	x	x	x	x	x
	R03AC14	Clenbuterol	no	no	no	no	no
	R03AC18	Indacaterol	x	x	x	x	x
	R03AC19	Olodaterol	no	x	no	no	no
SABA+SAMA	R03AL01 ***(R03AK03 in past)***	Fenoterol and ipratropium bromide	x	x	x	no	no

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	R03AL02 ***(R03AK04 in past)***	Salbutamol and ipratropium bromide	x	x	x	no	x
LABA+LAMA	R03AL03	Vilanterol and umeclidinium bromide	x	x	no	no	no
	R03AL04	Indacaterol and glycopyrronium bromide	x	x	x	x	x
	R03AL05	Formoterol and aclidinium bromide	x	x	no	no	no
LABA+ICS	R03AK06	Salmeterol and fluticasone	x	x	x	x	x
	R03AK07	Formoterol and budesonide	x	x	x	x	x
	R03AK08	Formoterol and beclomethasone	x	x	no	x	x
	R03AK09	Formoterol and momethasone	no	no	no	no	no
	R03AK10	Vilanterol and fluticasone furoate	x	x	no	no	no
	R03AK11	Formoterol and fluticasone	x	x	no	x	no
ICS	R03BA01	Beclometasone	x	x	x	x	x
	R03BA02	Budesonide	x	x	x	x	x
	R03BA03	Flunisolide	no	no	no	x	no
	R03BA04	Betamethasone	no	no	no	no	no
	R03BA05	Fluticasone	x	x	x	x	x
	R03BA06	Triamcinolone	no	no	no	no	no
	R03BA07	Mometasone	x	no	x	x	x
	R03BA08	Ciclesonide	x	x	x	x	x
	R03BA09	Fluticasone furoate		no			
other fixed combinations	R03AK01	Epinephrine and other drugs for obstructive airway diseases	no	no		no	no
	R03AK02	Isoprenaline and other drugs for obstructive airway diseases	no	no		no	no
	R03AK04	Salbutamol and sodium cromoglicate	x	no		no	x
	R03AK05	Reproterol and sodium cromoglicate	no	no		no	no
Xanthines	R03DA01	Diprophylline	no	no	no	x	no
	R03DA02	Choline theophyllinate	x	no	no	no	no

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	R03DA03	Proxyphylline	no	no	no	no	no
	R03DA04	Theophylline	x	x	x	x	x
	R03DA05	Aminophylline	x	no	x	x	no
	R03DA06	Etamiphylline	no	no	no	no	no
	R03DA07	Theobromine	x	no	no	no	no
	R03DA08	Bamifylline	no	no	no	x	no
	R03DA09	Acefylline piperazine	no	no	no	no	no
	R03DA10	Bufylline	no	no	no	no	no
	R03DA11	Doxofylline	no	no	no	x	no
	R03DA20	Combinations of xanthines	no	no	no	no	no
	R03DA51	Diprophylline, combinations	no	no	no	x	no
	R03DA54	Theophylline, combinations excluding psycholeptics	no	no	no	no	x
	R03DA55	Aminophylline, combinations	no	no	no	no	no
	R03DA57	Theobromine, combinations	no	no	no	no	no
	R03DA74	Theophylline, combinations with psycholeptics	no	no	no	no	no
Leukotriene receptor antagonists (LTRA)	R03DC01	Zafirlukast	x	no	x	x	x
	R03DC02	Pranlukast	no	no	no	no	no
	R03DC03	Montelukast	x	x	x	x	x
	R03DC04	Ibudilast	no	no	no	no	no
Oral phosphodiesterase- 4 (PDE-4) inhibitors	R03DX07	roflumilast	x	x	x	x	x
Oral ß$_2$-agonists	R03CC02	Salbutamol	x	x	x	x	x
	R03CC03	Terbutaline	x	no	x	no	x
	R03CC04	Fenoterol	no	no	no	no	no
	R03CC05	Hexoprenaline	no	no	no	no	no
	R03CC06	Isoetarine	no	no	no	no	no
	R03CC07	Pirbuterol	x	no	no	no	no
	R03CC08	Procaterol	no	no	no	no	no
	R03CC09	Tretoquinol	no	no	no	no	no
	R03CC10	Carbuterol	no	no	no	no	no
	R03CC11	Tulobuterol	x	no	no	no	no

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	R03CC12	Bambuterol	x	no	x	no	x
	R03CC13	Clenbuterol	no	no	no	x	no
	R03CC14	Reproterol	x	no	no	no	no
	R03CC53	Terbutaline, combinations	no	no	no	no	no
	R03CC90	Clenbuterol, combinations	no	no	no	no	no
Systemic glucocorticosteroids	H02AB01	Betamethasone	x	x	x	x	x
	H02AB02	Dexamethasone	x	x	x	x	x
	H02AB03	Fluocortolone	no	no	no	no	no
	H02AB04	Methylprednisolone	x	x	x	x	x
	H02AB05	Paramethasone	no	no	no	x	no
	H02AB06	Prednisolone	x	x	x	x	x
	H02AB07	Prednisone	x	x	x	x	x
	H02AB08	Triamcinolone	x	x	x	x	x
	H02AB09	Hydrocortisone	x	x	x	x	x
	H02AB10	Cortisone	x	x	no	x	no
	H02AB11	Prednylidene	no	no	no	no	no
	H02AB12	Rimexolone	no	no	no	no	no
	H02AB13	Deflazacort	x	no	no	x	no
	H02AB14	Cloprednol	no	no	no	no	no
	H02AB15	Meprednisone	no	no	no	no	no
	H02AB17	Cortivazol	no	no	no	no	no
	H02AB30	Combinations of glucocorticoids	no	no	no	no	no
	H02AB56	Prednisolone, combinations	no	no	no	no	no
	H02AB57	Prednisone, combinations	no	no	no	no	no
	H02AB90	Flumetasone	no	no	no	no	no

Annex 2.4 – COPD definition

According to GOLD (Global initiative of lung disease), COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a postbronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD. (Cazzola et al 2011)

COPD will be identified within the databases both by COPD disease specific codes and via free text search for those databases where free text is available.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease, unspecified	J44.9			R95
Chronic obstructive lung disease			H3*...	
Chronic obstructive airways disease			H3z..*	
Other chronic obstructive pulmonary disease	J44			
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31*	
Other specified chronic obstructive airways disease			H3y..*	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		H3y1.00*	
Mild chronic obstructive pulmonary disease			H36..00*	
Moderate chronic obstructive pulmonary disease			H37..00*	
Severe chronic obstructive pulmonary disease			H38..00*	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Very severe chronic obstructive pulmonary disease			H39..00*	
chronic obstructive pulmonary disease and allied conditions		491.2 and 496		
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.00.*	
COPD review/monitoring			66Y.*	
COPD quality indicators			9h5*	

*Read codes selected based on QoF codes for COPD as applied in the UK

COPD severity will be assessed at the index date for the three different exposure cohorts on the basis of spirometry data or on the basis of a severity classification if spirometry is not available.

If spirometry is available:

Severity of COPD will be determined by spirometry, according to GOLD guidelines:

Mild COPD (GOLD stage I): $FEV_1/FVC<70\%$ and FEV_1 predicted >= 80%

Moderate COPD (GOLD stage II): $FEV_1/FVC<70\%$ and $50\%<=FEV_1<80\%$ predicted

Severe COPD (GOLD stage III): $FEV_1/FVC<70\%$ and $30\%<=FEV_1<50\%$ predicted

Very severe COPD (GOLD stage IV): $FEV_1/FVC<70\%$ and $FEV_1<30\%$ predicted or $FEV_1<50\%$ predicted and chronic respiratory failure.

The most recently performed spirometry prior to the index date (for all 3 cohorts) will be considered. In addition, in accordance with the updated GOLD guidelines (updated GOLD 2011), patients will be further stratified upon the previous history of exacerbations (no, one or ≥ two exacerbations in the year prior to the index date [time of first prescription]). (Cazzola et al 2011) A moderate COPD exacerbation is defined as need for oral corticosteroids and/or systemic antibiotics for COPD. A severe COPD exacerbation is defined as hospitalisation because of COPD exacerbation.

Since the COPD Assessment Test (CAT) is not performed routinely in clinical practice, and since a CAT score < 10 occurs only in the setting of screening programs in general populations, all patients will be considered as COPD GOLD B or D patients: COPD GOLD B if FEV1 > 50% AND a history of ≤ 1 exacerbation in the previous year; COPD GOLD D if FEV1 ≤ 50% OR a history of ≥ 2 exacerbations in the previous year.

If spirometry is not available:

COPD severity will be categorised according to published literature on COPD severity scores using data from GP or health care databases. The COPD severity assessed closed to the index date (for all 3 cohorts) will be considered.

Mild: Patients initially diagnosed with COPD

Moderate: Patients on regular treatment (defined as at least 2 prescriptions of the same drug group within 6 months) with inhaled/oral bronchodilators, xanthines or combination therapy. Patients are considered to have moderate COPD from the time of the second prescription on.

Severe: Patients with any of the following:

- hospitalized for COPD during the past 365 days (prior to the index date)
- requiring 3 or more courses of antibiotics for the treatment of respiratory infections or COPD exacerbations in the past 365 days (prior to the index date)
- two or more courses of systemic corticosteroids for the treatment of COPD exacerbations in the past 365 days (prior to the index date)
- long term use of systemic corticosteroids in the past 365 days for the treatment of COPD (prior to the index date)

Very severe: Patients requiring chronic oxygen therapy.

Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of QVA149+codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics

For the DUS reports, we are interested in the indication of use of QVA149. As GPs often use the terms COPD, chronic bronchitis and emphysema interchangeably, we will also consider disease specific codes for chronic bronchitis and emphysema. Thus codes for indication of use related to COPD are broader than the codes used to define COPD (Annex 2.4).

Terms	ICD10	ICD9CM	Read Codes	ICPC
COPD exacerbation	J44.0		66Yd.00	
	J44.1		66Ye.00	
			66Yf.00	
			8H2R.00	
			H3y1.00	
			H312200	
Chronic obstructive pulmonary disease disturbs sleep			66Yg.00	
Chronic obstructive pulmonary disease does not disturb sleep			66Yh.00	
Attends respiratory support group			66YH.00	
COPD self-management plan given			66YI.00	
Multiple COPD emergency hospitalisations			66Yi.00	
Chronic obstructive pulmonary disease follow-up/monitoring			66YL.00	
			66YL.11	
			66YL.12	
			66YM.00	
			66YS.00	
			66YT.00	
COPD quality indicators			9h5..00	
			9h51.00	
			9h52.00	
Chronic bronchitis		491*	H31..00	R91
Simple and mucopurulent chronic bronchitis	J41			
Unspecified chronic bronchitis	J42			
Simple chronic bronchitis			H310.00	
Simple chronic bronchitis NOS			H310z00	
Mucopurulent chronic bronchitis			H311.00	
Purulent chronic bronchitis			H311000	
Fetid chronic bronchitis			H311100	
Mucopurulent chronic bronchitis NOS			H311z00	
Obstructive chronic bronchitis			H312.00	
Chronic wheezy bronchitis			H312011	
Emphysematous bronchitis			H312100	
Mixed simple and mucopurulent chronic bronchitis			H313.00	
Other chronic bronchitis			H31y.00	
Other chronic bronchitis NOS			H31yz00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic bronchitis NOS			H31z.00	
Bronchitis, not specified as acute or chronic	J40	490		
Emphysema	J43	492*	H32..00	R95
interstitial emphysema		518.1		
Compensatory emphysema		518.2		
Chronic bullous emphysema			H320.00	
Segmental bullous emphysema			H320000	
Zonal bullous emphysema			H320100	
Giant bullous emphysema			H320200	
Bullous emphysema with collapse			H320300	
Chronic bullous emphysema NOS			H320z00	
Panlobular emphysema			H321.00	
Centrilobular emphysema			H322.00	
Other emphysema			H32y.00	
Acute vesicular emphysema			H32y000	
Atrophic (senile) emphysema			H32y100	
MacLeod's unilateral emphysema			H32y200	
Other emphysema NOS			H32yz00	
Emphysema NOS			H32z.00	

Annex 2.6 – Concomitant medication use

Anticholinergic drugs

Antipsychotic drugs **(N05A)**

N05AA Phenothiazines with aliphatic side-chain

N05AA01 Chlorpromazine

N05AA02 Levomepromazine

N05AA03 Promazine

N05AA04 Acepromazine

N05AA05 Triflupromazine

N05AA06 Cyamemazine

N05AA07 Chlorproethazine

N05AB Phenothiazines with piperazine structure

N05AB01 Dixyrazine

N05AB02 Fluphenazine

N05AB03 Perphenazine

N05AB04 Prochlorperazine

N05AB05 Thiopropazate

N05AB06 Trifluoperazine

N05AB07 Acetophenazine

N05AB08 Thioproperazine

N05AB09 Butaperazine

N05AB10 Perazine

N05AC Phenothiazines with piperidine structure

N05AC01 Periciazine

N05AC02 Thioridazine

N05AC03 Mesoridazine

N05AC04 Pipotiazine

N05AD Butyrophenone derivatives

N05AD01 Haloperidol

N05AD02 Trifluperidol

N05AD03 Melperone

N05AD04 Moperone

N05AD05 Pipamperone

N05AD06 Bromperidol

N05AD07 Benperidol

N05AD08 Droperidol

N05AD09 Fluanisone

N05AD90 Azaperone

N05AE Indole derivatives

N05AE01 Oxypertine

N05AE02 Molindone

N05AE03 Sertindole

N05AE04 Ziprasidone

N05AF Thioxanthene derivative

N05AF01 Flupentixol

N05AF02 Clopenthixol

N05AF03 Chlorprothixene

N05AF04 Thiothixene

N05AF05 Zuclopenthixol

N05AG Diphenylbutylpiperidine derivatives

N05AG01 Fluspirilene

N05AG02 Pimozide

N05AG03 Penfluridol

N05AH Diazepines, oxazepines, thiazepines and oxepines

N05AH01 Loxapine

N05AH02 Clozapine

N05AH03 Olanzapine

N05AH04 Quetiapine

N05AH05 Asenapine

N05AH06 Clotiapine

N05AK Neuroleptics, in tardive dyskinesia

N05AL Benzamides

N05AL01 Sulpiride

N05AL02 Sultopride

N05AL03 Tiapride

N05AL04 Remoxipride

N05AL05 Amisulpride

N05AL06 Veralipride

N05AL07 Levosulpiride

N05AN Lithium

N05AN01 Lithium

N05AX Other antipsychotics

N05AX07 Prothipendyl

N05AX08 Risperidone

N05AX10 Mosapramine

N05AX11 Zotepine

N05AX12 Aripiprazole

N05AX13 Paliperidone

N05AX14 Iloperidone

N05AX90 Amperozide

Tricyclic and tetracyclic antidepressant agents **(N06A)**

N06AA Non-selective monoamine reuptake inhibitors

N06AA01 Desipramine

N06AA02 Imipramine

N06AA03 Imipramine oxide

N06AA04 Clomipramine

N06AA05 Opipramol

N06AA06 Trimipramine

N06AA07 Lofepramine

N06AA08 Dibenzepin

N06AA09 Amitriptyline

N06AA10 Nortriptyline

N06AA11 Protriptyline

N06AA12 Doxepin

N06AA13 Iprindole

N06AA14 Melitracen

N06AA15 Butriptyline

N06AA16 Dosulepin

N06AA17 Amoxapine

N06AA18 Dimetacrine

N06AA19 Amineptine

N06AA21 Maprotiline

N06AA23 Quinupramine

N06AX Other antidepressants

N06AX01 Oxitriptan

N06AX02 Tryptophan

N06AX03 Mianserin

N06AX04 Nomifensine

N06AX05 Trazodone

N06AX06 Nefazodone

N06AX07 Minaprine

N06AX08 Bifemelane

N06AX09 Viloxazine

N06AX10 Oxaflozane

N06AX11 Mirtazapine

N06AX12 Bupropion

N06AX13 Medifoxamine

N06AX14 Tianeptine

N06AX15 Pivagabine

N06AX16 Venlafaxine

N06AX17 Milnacipran

N06AX18 Reboxetine

N06AX19 Gepirone

N06AX21 Duloxetine

N06AX22 Agomelatine

N06AX23 Desvenlafaxine

N06AX24 Vilazodone

N06AX25 Hyperici herba

N06AX90 Selegiline

Disopyramide **(C01BA)**

C01BA03 Disopyramide

Antispasmodics **(A03A)**

A03AA Synthetic anticholinergics, esters with tertiary amino group

A03AA01 Oxyphencyclimine

A03AA03 Camylofin

A03AA04 Mebeverine

A03AA05 Trimebutine

A03AA06 Rociverine

A03AA07 Dicycloverine

A03AA08 Dihexyverine

A03AA09 Difemerine

A03AA30 Piperidolate

A03AB Synthetic anticholinergics, quaternary ammonium compounds

A03AB01 Benzilone

A03AB02 Glycopyrronium

A03AB03 Oxyphenonium

A03AB04 Penthienate

A03AB05 Propantheline

A03AB06 Otilonium bromide

A03AB07 Methantheline

A03AB08 Tridihexethyl

A03AB09 Isopropamide

A03AB10 Hexocyclium

A03AB11 Poldine

A03AB12 Mepenzolate

A03AB13 Bevonium

A03AB14 Pipenzolate

A03AB15 Diphemanil

A03AB16 (2-benzhydryloxyethyl)diethyl-methylammonium iodide

A03AB17 Tiemonium iodide

A03AB18 Prifinium bromide

A03AB19 Timepidium bromide

A03AB21 Fenpiverinium

A03AB53 Oxyphenonium, combinations

A03AB90 Benzetimide

A03AB92 Carbachol

A03AB93 Neostigmin

Anti Parkinson drugs

N04A Anticholinergic agents

N04AA Tertiary amines

N04AA01 Trihexyphenidyl

N04AA02 Biperiden

N04AA03 Metixene

N04AA04 Procyclidine

N04AA05 Profenamine

N04AA08 Dexetimide

N04AA09 Phenglutarimide

N04AA10 Mazaticol

N04AA11 Bornaprine

N04AA12 Tropatepine

N04AB Ethers chemically close to antihistamines

N04AB01 Etanautine

N04AB02 Orphenadrine (chloride)

N04AC Ethers of tropine or tropine derivatives

N04AC01 Benzatropine

N04AC30 Etybenzatropine

Choline-esterase inhibitors **(N07A)**

N07AA Anticholinesterases

N07AA01 Neostigmine

N07AA02 Pyridostigmine

N07AA03 Distigmine

N07AA30 Ambenonium

N07AA51 Neostigmine, combinations

Atropine **(A03BA)**

A03BA01 Atropine

H1-antihistamines **(R06A)**

R06AA Aminoalkyl ethers

R06AA01 Bromazine

R06AA02 Diphenhydramine

R06AA04 Clemastine

R06AA06 Chlorphenoxamine

R06AA07 Diphenylpyraline

R06AA08 Carbinoxamine

R06AA09 Doxylamine

R06AA52 Diphenhydramine, combinations

R06AA54 Clemastine, combinations

R06AA56 Chlorphenoxamine, combinations

R06AA57 Diphenylpyraline, combinations

R06AA59 Doxylamine, combinations

R06AB Substituted alkylamines

R06AB01 Brompheniramine

R06AB02 Dexchlorpheniramine

R06AB03 Dimetindene

R06AB04 Chlorphenamine

R06AB05 Pheniramine

R06AB06 Dexbrompheniramine

R06AB07 Talastine

R06AB51 Brompheniramine, combinations

R06AB52 Dexchlorpheniramine, combinations

R06AB54 Chlorphenamine, combinations

R06AB56 Dexbrompheniramine, combinations

R06AC Substituted ethylene diamines

R06AC01 Mepyramine

R06AC02 Histapyrrodine

R06AC03 Chloropyramine

R06AC04 Tripelennamine

R06AC05 Methapyrilene

R06AC06 Thonzylamine

R06AC52 Histapyrrodine, combinations

R06AC53 Chloropyramine, combinations

R06AD Phenothiazine derivatives

R06AD01 Alimemazine

R06AD02 Promethazine

R06AD03 Thiethylperazine

R06AD04 Methdilazine

R06AD05 Hydroxyethylpromethazine

R06AD06 Thiazinam

R06AD07 Mequitazine

R06AD08 Oxomemazine

R06AD09 Isothipendyl

R06AD52 Promethazine, combinations

R06AD55 Hydroxyethylpromethazine, combinations

R06AE Piperazine derivatives

R06AE01 Buclizine

R06AE03 Cyclizine

R06AE04 Chlorcyclizine

R06AE05 Meclozine

R06AE06 Oxatomide

R06AE07 Cetirizine

R06AE09 Levocetirizine

R06AE51 Buclizine, combinations

R06AE53 Cyclizine, combinations

R06AE55 Meclozine, combinations

R06AK Combinations of antihistamines

R06AX Other antihistamines for systemic use

R06AX01 Bamipine

R06AX02 Cyproheptadine

R06AX03 Thenalidine

R06AX04 Phenindamine

R06AX05 Antazoline

R06AX07 Triprolidine

R06AX08 Pyrrobutamine

R06AX09 Azatadine

R06AX11 Astemizole

R06AX12 Terfenadine

R06AX13 Loratadine

R06AX15 Mebhydrolin

R06AX16 Deptropine

R06AX17 Ketotifen

R06AX18 Acrivastine

R06AX19 Azelastine

R06AX21 Tritoqualine

R06AX22 Ebastine

R06AX23 Pimethixene

R06AX24 Epinastine

R06AX25 Mizolastine

R06AX26 Fexofenadine

R06AX27 Desloratadine

R06AX28 Rupatadine

R06AX29 Bilastine

R06AX53 Thenalidine, combinations

R06AX58 Pyrrobutamine, combinations

Anticholinergics for treatment of overactive bladder

G04BD Urinary antispasmodics

G04BD01 Emepronium

G04BD02 Flavoxate

G04BD03 Meladrazine

G04BD04 Oxybutynin

G04BD05 Terodiline

G04BD06 Propiverine

G04BD07 Tolterodine

G04BD08 Solifenacin

G04BD09 Trospium

G04BD10 Darifenacin

G04BD11 Fesoterodine

Systemic glucocorticosteroids

H02AB Glucocorticoids

H02AB01 Betamethasone

H02AB02 Dexamethasone

H02AB03 Fluocortolone

H02AB04 Methylprednisolone

H02AB05 Paramethasone

H02AB06 Prednisolone

H02AB07 Prednisone

H02AB08 Triamcinolone

H02AB09 Hydrocortisone

H02AB10 Cortisone

H02AB11 Prednylidene

H02AB12 Rimexolone

H02AB13 Deflazacort

H02AB14 Cloprednol

H02AB15 Meprednisone

H02AB17 Cortivazol

H02AB30 Combinations of glucocorticoids

H02AB56 Prednisolone, combinations

H02AB57 Prednisone, combinations

H02AB90 Flumetasone

Antibiotics (if given for the treatment of lower respiratory tract infections = acute bronchitis, pneumonia, COPD) (J01)

J01AA Tetracyclines (J01A)

J01AA01 Demeclocycline

J01AA02 Doxycycline

J01AA03 Chlortetracycline

J01AA04 Lymecycline

J01AA05 Metacycline

J01AA06 Oxytetracycline

J01AA07 Tetracycline

J01AA08 Minocycline

J01AA09 Rolitetracycline

J01AA10 Penimepicycline

J01AA11 Clomocycline

J01AA12 Tigecycline

J01AA20 Combinations of tetracyclines

J01AA53 Chlortetracycline, combinations

J01AA56 Oxytetracycline, combinations

J01B Amphenicols (J01B)

J01BA

J01BA01 Chloramphenicol

J01BA02 Thiamphenicol

J01BA52 Thiamphenicol, combinations

J01BA90 Florfenicol

J01BA99 Amphenicols, combinations

J01C Beta-lactam antibacterials, penicillins (J01C)

J01CA Penicillins with extended spectrum

J01CA01 Ampicillin

J01CA02 Pivampicillin

J01CA03 Carbenicillin

J01CA04 Amoxicillin

J01CA05 Carindacillin

J01CA06 Bacampicillin

J01CA07 Epicillin

J01CA08 Pivmecillinam

J01CA09 Azlocillin

J01CA10 Mezlocillin

J01CA11 Mecillinam

J01CA12 Piperacillin

J01CA13 Ticarcillin

J01CA14 Metampicillin

J01CA15 Talampicillin

J01CA16 Sulbenicillin

J01CA17 Temocillin

J01CA18 Hetacillin

J01CA19 Aspoxicillin

J01CA20 Combinations

J01CA51 Ampicillin, combinations

J01CE Beta-lactamase-sensitive penicillin

J01CE01 Benzylpenicillin

J01CE02 Phenoxymethylpenicillin

J01CE03 Propicillin

J01CE04 Azidocillin

J01CE05 Pheneticillin

J01CE06 Penamecillin

J01CE07 Clometocillin

J01CE08 Benzathine benzylpenicillin

J01CE09 Procaine benzylpenicillin

J01CE10 Benzathine phenoxymethylpenicillin

J01CE30 Combinations

J01CE90 Penethamate hydroiodide

J01CE91 Benethamine penicillin

J01CF Beta-lactamase-resistant penicillins

J01CF01 Dicloxacillin

J01CF02 Cloxacillin

J01CF03 Methicillin

J01CF04 Oxacillin

J01CF05 Flucloxacillin

J01CF06 Nafcillin

J01CG Beta-lactamase inhibitors

J01CG01 Sulbactam

J01CG02 Tazobactam

J01CR Combinations of penicillins, including beta-lactamase inhibitors

J01CR01 Ampicillin and enzyme inhibitor

J01CR02 Amoxicillin and enzyme inhibitor

J01CR03 Ticarcillin and enzyme inhibitor

J01CR04 Sultamicillin

J01CR05 Piperacillin and enzyme inhibitor

J01CR50 Combinations of penicillins

J01D Other beta-lactam antibacterials (J01D)

J01DB First-generation cephalosporins

J01DB01 Cefalexin

J01DB02 Cefaloridine

J01DB03 Cefalotin

J01DB04 Cefazolin

J01DB05 Cefadroxil

J01DB06 Cefazedone

J01DB07 Cefatrizine

J01DB08 Cefapirin

J01DB09 Cefradine

J01DB10 Cefacetrile

J01DB11 Cefroxadine

J01DB12 Ceftezole

J01DC Second-generation cephalosporins

J01DC01 Cefoxitin

J01DC02 Cefuroxime

J01DC03 Cefamandole

J01DC04 Cefaclor

J01DC05 Cefotetan

J01DC06 Cefonicide

J01DC07 Cefotiam

J01DC08 Loracarbef

J01DC09 Cefmetazole

J01DC10 Cefprozil

J01DC11 Ceforanide

J01DC12 Cefminox

J01DC13 Cefbuperazone

J01DC14 Flomoxef

J01DD Third-generation cephalosporins

J01DD01 Cefotaxime

J01DD02 Ceftazidime

J01DD03 Cefsulodin

J01DD04 Ceftriaxone

J01DD05 Cefmenoxime

J01DD06 Latamoxef

J01DD07 Ceftizoxime

J01DD08 Cefixime

J01DD09 Cefodizime

J01DD10 Cefetamet

J01DD11 Cefpiramide

J01DD12 Cefoperazone

J01DD13 Cefpodoxime

J01DD14 Ceftibuten

J01DD15 Cefdinir

J01DD16 Cefditoren

J01DD17 Cefcapene

J01DD54 Ceftriaxone, combinations

J01DD62 Cefoperazone, combinations

J01DD90 Ceftiofur

J01DD91 Cefovecin

J01DE Fourth-generation cephalosporins

J01DE01 Cefepime

J01DE02 Cefpirome

J01DE03 Cefozopran

J01DE90 Cefquinome

J01DF Monobactams

J01DF01 Aztreonam

J01DF02 Carumonam

J01DH Carbapenems

J01DH02 Meropenem

J01DH03 Ertapenem

J01DH04 Doripenem

J01DH05 Biapenem

J01DH51 Imipenem and enzyme inhibitor

J01DH55 Panipenem and betamipron

J01DI Other cephalosporins and penems

J01DI01 Ceftobiprole medocaril

J01DI02 Ceftaroline fosamil

J01DI03 Faropenem

J01E Sulfonamides and trimethoprim (J01E)

J01EA Trimethoprim and derivatives

J01EA01 Trimethoprim

J01EA02 Brodimoprim

J01EA03 Iclaprim

J01EB Short-acting sulfonamides

J01EB01 Sulfaisodimidine

J01EB02 Sulfamethizole

J01EB03 Sulfadimidine

J01EB04 Sulfapyridine

J01EB05 Sulfafurazole

J01EB06 Sulfanilamide

J01EB07 Sulfathiazole

J01EB08 Sulfathiourea

J01EB20 Combinations

J01EC Intermediate-acting sulfonamides

J01EC01 Sulfamethoxazole

J01EC02 Sulfadiazine

J01EC03 Sulfamoxole

J01EC20 Combinations

J01ED Long-acting sulfonamides

J01ED01 Sulfadimethoxine

J01ED02 Sulfalene

J01ED03 Sulfametomidine

J01ED04 Sulfametoxydiazine

J01ED05 Sulfamethoxypyridazine

J01ED06 Sulfaperin

J01ED07 Sulfamerazine

J01ED08 Sulfaphenazole

J01ED09 Sulfamazon

J01ED20 Combinations

J01EE Combinations of sulfonamides and trimethoprim, including derivatives

J01EE01 Sulfamethoxazole and trimethoprim

J01EE02 Sulfadiazine and trimethoprim

J01EE03 Sulfametrole and trimethoprim

J01EE04 Sulfamoxole and trimethoprim

J01EE05 Sulfadimidine and trimethoprim

J01EE06 Sulfadiazine and tetroxoprim

J01EE07 Sulfamerazine and trimethoprim

J01EQ Sulfonamides

J01EQ01 Sulfapyrazole

J01EQ02 Sulfamethizole

J01EQ03 Sulfadimidine

J01EQ04 Sulfapyridine

J01EQ05 Sulfafurazole

J01EQ06 Sulfanilamide

J01EQ07 Sulfathiazole

J01EQ08 Sulfaphenazole

J01EQ09 Sulfadimethoxine

J01EQ10 Sulfadiazine

J01EQ11 Sulfamethoxazole

J01EQ12 Sulfachlorpyridazine

J01EQ13 Sulfadoxine

J01EQ14 Sulfatroxazol

J01EQ15 Sulfamethoxypyridazine

J01EQ16 Sulfazuinoxaline

J01EQ17 Sulfamerazine

J01EQ18 Sulfamonomethoxine

J01EQ19 Sulfalene

J01EQ21 Sulfacetamide

J01EQ30 Combinations of sulfonamides

J01EQ59 Sulfadimethoxine, combinations

J01EW Combinations of sulfonamides and trimethoprim, including derivatives

J01EW03 Sulfadimidine and trimethoprim

J01EW09 Sulfadimethoxine and trimethoprim

J01EW10 Sulfadiazine and trimethoprim

J01EW11 Sulfamethoxazole and trimethoprime

J01EW12 Sulfachlorpyridazine and trimethoprim

J01EW13 Sulfadoxine and trimethoprim

J01EW14 Sulfatroxazol and trimethoprim

J01EW15 Sulfamethoxypyridazine and trimethoprim

J01EW16 Sulfaquinoxaline and trimethoprim

J01EW17 Sulfamonomethoxine and trimethoprim

J01EW18 Sulfamerazine and trimethoprim

J01EW30 Combinations of sulfonamides and trimethoprim

J01F Macrolides, lincosamides and streptogramins (J01F)

J01FA Macrolides

J01FA01 Erythromycin

J01FA02 Spiramycin

J01FA03 Midecamycin

J01FA05 Oleandomycin

J01FA06 Roxithromycin

J01FA07 Josamycin

J01FA08 Troleandomycin

J01FA09 Clarithromycin

J01FA10 Azithromycin

J01FA11 Miocamycin

J01FA12 Rokitamycin

J01FA13 Dirithromycin

J01FA14 Flurithromycin

J01FA15 Telithromycin

J01FA90 Tylosin

J01FA91 Tilmicosin

J01FA92 Tylvalosin

J01FA93 Kitasamycin

J01FA94 Tulathromycin

J01FA95 Gamithromycin

J01FA96 Tildipirosin

J01FF Lincosamides

J01FF01 Clindamycin

J01FF02 Lincomycin

J01FF52 Lincomycin, combinations

J01FG Streptogramins

J01FG01 Pristinamycin

J01FG02 Quinupristin/dalfopristin

J01FG90 Virginiamycin

J01G Aminoglycoside antibacterials (J01G)

J01GA Streptomycins

J01GA01 Streptomycin

J01GA02 Streptoduocin

J01GA90 Dihydrostreptomycin

J01GB Other aminoglycosides

J01GB01 Tobramycin

J01GB03 Gentamicin

J01GB04 Kanamycin

J01GB05 Neomycin

J01GB06 Amikacin

J01GB07 Netilmicin

J01GB08 Sisomicin

J01GB09 Dibekacin

J01GB10 Ribostamycin

J01GB11 Isepamicin

J01GB12 Arbekacin

J01GB13 Bekanamycin

J01GB90 Apramycin

J01GB91 Framycetin

J01M Quinolone antibacterials (J01M)

J01MA Fluoroquinolones

J01MA01 Ofloxacin

J01MA02 Ciprofloxacin

J01MA03 Pefloxacin

J01MA04 Enoxacin

J01MA05 Temafloxacin

J01MA06 Norfloxacin

J01MA07 Lomefloxacin

J01MA08 Fleroxacin

J01MA09 Sparfloxacin

J01MA10 Rufloxacin

J01MA11 Grepafloxacin

J01MA12 Levofloxacin

J01MA13 Trovafloxacin

J01MA14 Moxifloxacin

J01MA15 Gemifloxacin

J01MA16 Gatifloxacin

J01MA17 Prulifloxacin

J01MA18 Pazufloxacin

J01MA19 Garenoxacin

J01MA21 Sitafloxacin

J01MA90 Enrofloxacin

J01MA92 Danofloxacin

J01MA93 Marbofloxacin

J01MA94 Difloxacin

J01MA95 Orbifloxacin

J01MA96 Ibafloxacin

J01MA97 Pradofloxacin

J01MB Other quinolones

J01MB01 Rosoxacin

J01MB02 Nalidixic acid

J01MB03 Piromidic acid

J01MB04 Pipemidic acid

J01MB05 Oxolinic acid

J01MB06 Cinoxacin

J01MB07 Flumequine

J01MQ Quinoxalines

J01MQ01 Olaquindox

J01R Combinations of antibacterials (J01R)

J01RA Combinations of antibacterials

J01RA01 Penicillins, combinations with other antibacterials

J01RA02 Sulfonamides, combinations with other antibacterials (excluding trimethoprim)

J01RA03 Cefuroxime, combinations with other antibacterials

J01RA04 Spiramycin, combinations with other antibacterials

J01RA90 Tetracyclines, combinations with other antibacterials

J01RA91 Macrolides, combinations with other antibacterials

J01RA92 Amphenicols, combinations with other antibacterials

J01RA94 Lincosamides, combinations with other antibacterials

J01RA95 Polymyxins, combinations with other antibacterials

J01RA96 Quinolones, combinations with other antibacterials

J01RA97 Aminoglycosides, combinations with other antibacterials

J01RV Combinations of antibacterials and other substances

J01RV01 Antibacterials and corticosteroids

J01X Other antibacterials (J01X)

J01XA Glycopeptide antibacterials

J01XA01 Vancomycin

J01XA02 Teicoplanin

J01XA03 Telavancin

J01XA04 Dalbavancin

J01XA05 Oritavancin

J01XB Polymyxins

J01XB01 Colistin

J01XB02 Polymyxin B

J01XC Steroid antibacterials

J01XC01 Fusidic acid

J01XD Imidazole derivatives

J01XD01 Metronidazole

J01XD02 Tinidazole

J01XD03 Ornidazole

J01XE Nitrofuran derivatives

J01XE01 Nitrofurantoin

J01XE02 Nifurtoinol

QJ01XE90 Furazolidine

QJ01XQ Pleuromutilins

QJ01XQ01 Tiamulin

QJ01XQ02 Valnemulin

J01XX Other antibacterials

J01XX01 Fosfomycin

J01XX02 Xibornol

J01XX03 Clofoctol

J01XX04 Spectinomycin

J01XX05 Methenamine

J01XX06 Mandelic acid

J01XX07 Nitroxoline

J01XX08 Linezolid

J01XX09 Daptomycin

J01XX10 Bacitracin

QJ01XX55 Methenamine, combinations

QJ01XX93 Furaltadone

QJ01XX95 Novobiocin

Annex 2.7 – Data sources

IPCI Database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Center. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout The Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout The Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care.

The database contains information on about 2.2 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimens, strength and indication are entered into the computer (Vlug et al 1999). The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO (WHO 2008).

As this is a primary care database, information on specialist prescribing, drug dispensing and actual drug intake is missing.

IPCI is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

THIN Database

The Health Improvement Network (THIN) is a database of primary care medical records from the United Kingdom. General practitioners are trained to complete their medical records using the Vision general practice computer system (InPractice Systems, London, UK). This electronic record serves as the primary medical records for the practice.

Data recorded in THIN include demographics, details from general practitioners' visits such as medical diagnoses and prescriptions written by the general practitioners, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record. Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted by Lewis et al which concluded that "THIN data that are collected outside of the Clinical Practice Research Datalink (CPRD) appear as valid as the data collected as part of the CPRD (Lewis et al 2007).

As the primary aim of the collection of data in the THIN database is patient management, data will reflect only those events that are deemed to be relevant to patient's care. In addition; use of THIN data is not appropriate in studies where individual ethnicity, occupation, employment, and/or socio-economic status are important variables. As for all prescription databases, OTC drug use and non-compliance to medication prescriptions might be an issue. As the average follow-up within the THIN database is 7.3 years, the THIN database is not suitable to conduct long-term follow-up studies.

THIN is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

Aarhus Database

The Aarhus University Prescription Database comprises clinical and prescription data on the population of former North-Jutland, Aarhus, Rinkjebing and Viborg counties, which since 2007 are called the Central Denmark Region and the North Denmark Region. This population covers a total of 1.4 million inhabitants and is representative of the population of Denmark (Ehrenstein et al 2010) Data available on these subjects comprise their eligibility, dispensing data, hospitalizations and procedures and the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures are registered. These databases have been used in numerous studies and are proven valid for pharmacoepidemiological research (Sorensen et al 1994).

Dose must be inferred from the strength, assuming a once daily administration for QVA149 and according the dosing regimens of the respective Summary of Product Characteristics of the other drugs. The main drawbacks of the Aarhus University Prescription Database are a lack of nationwide coverage and the absence of data of certain medication types (non-reimbursed drugs, OTC drugs or drugs dispensed directly to hospital patients or outpatient clinics).

HSD CSD Longitudinal Patient Database

The Italian arm of the study uses the Health Search CSD Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. It was established in 1998 by the Italian College of General Practitioners (Filippi et al 2005). The HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.7 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification system (WHO 2008). To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and

mortality rates (Cricelli et al 2003). The HSD complies with EU, guidelines on the use of medical data for research. The HSD has been used as data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care (Cazzola et al 2011). Approval for use of data is obtained from the Italian College of General Practitioners.

Dose must be inferred from the strength, assuming a once daily administration for QVA149 and according to the dosing regimens of the respective SmPC for the other drugs. Around 50% of prescription dosage is also imputed by GPs.

HSD is listed under the ENCePP resources database. (www.encepp.eu/encepp/resourcesDatabase.jsp)

SIDIAP Database

General practitioners (GPs) play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.6 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes. Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP Database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil Mdel et al 2011).