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NVA237 / Glycopyrronium bromide

Non-interventional Final Study Report

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Multinational, multi-database drug utilization study of inhaled NVA237 in Europe

Redacted Report

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Marketing authorization holder	Novartis Europharm Ltd Frimley Business Park Camberley GU16 7SR United Kingdom
Joint PASS	No
Research question and objectives	In the context of the NVA237 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. The objectives of this study are to estimate the subpopulation with cardio- and cerebrovascular co-morbidity and to identify patient groups with missing information as per the Risk Management Plan.
Country(-ies) of study	United Kingdom, Denmark, Italy, The Netherlands, Spain

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1 Abstract

Title

Multinational, multi-database drug utilization study of inhaled NVA237 in Europe

Non-interventional Final Study Report

Date of abstract:
28 April 2016

Name and affiliation of main author:
[redacted]

Keywords

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

Rationale and background

NVA237 (glycopyrronium bromide) is a long acting muscarinic antagonist (LAMA) which was approved in Europe in September 2012 as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). In the context of the NVA237 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 co-morbidity and to identify patient groups with missing information as per the risk management plan (RMP).

Research question and objectives

With this cohort study, we aim to determine the proportion of patients using NVA237 with cardiovascular or cerebrovascular co-morbidity, with conditions corresponding to patient groups defined in the 'Missing information' section of the RMP, with high risk treatment conditions, use of NVA237 in patients younger than 18 years or in patients without a diagnosis of COPD, and with an uninterrupted use for more than one year .

Study design

Multinational, multi-database cohort study in new users of NVA237.

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 28 months of data collection, namely from 01 November 2012 until 01 March 2015.

Subjects and study size, including dropouts

From the respective five databases, we selected patients during the study period (01 November 2012 until 01 March 2015 for this final report) who had at least one year of valid database history and were newly prescribed/dispensed NVA237 (i.e. did not have a prescription/dispensation of NVA237 during the year prior to this).

Variables and data sources

Patient characteristics included demographics (age, gender), indication of use, prescribed daily dosage, concomitant use of other respiratory medications, concomitant use of medications with anticholinergic properties, underlying co-morbidities (i.e., renal impairment, narrow angle glaucoma, urinary retention or symptomatic bladder outflow obstruction, cardiovascular and cerebrovascular disease, and liver disease), lifestyle factors, and COPD characteristics (COPD duration and COPD severity). Patient characteristics were summarized by means of descriptive statistics at the time of the index date (= date of the first NVA237 prescription during the study period).

Off-label use was presented separately with respect to age and indication. The proportion of patients with a 'potential' off-label indication was calculated as the number of patients with an indication other than COPD or COPD and asthma divided by the overall number of NVA237 initiators for whom information on indication of use was available.

Results

During the study period, 13,707 patients with newly prescribed NVA237 were identified (i.e. 2,159 in THIN, 1,025 in IPCI, 1,424 in Aarhus, 2,873 in HSD and 6,226 in SIDIAP). These patients were comparable between the five databases in terms of age (median age between 69 and 74). Overall, NVA237 was prescribed more frequently to men (59.9%) than women. The majority of patients had moderate or severe COPD based on spirometry data. The number of patients who used NVA237 for a consecutive period of more than 1 year was 1,261 (9.2%) and the number of patients with at least 1 year of follow up following start of NVA237 was 5,952 (43.3%).

In the database-pooled population, the proportion of cardiovascular comorbidity was as following: history of cardiac arrhythmia (11.5%), heart failure (9.2%), unstable ischemic heart disease (6.6%), angina pectoris (7.4%), and myocardial infarction (5.8%). The number of patients with malignant ventricular arrhythmia was low, namely less than 1.5%. Data were comparable across databases apart from the prevalence of heart failure which ranged between 7.1-14.2% and angina pectoris which was low in Italy and Spain (around 3%) and higher in the other databases (range 13.1-16.7%).

The proportion of patients with a history of stroke was 6.8% and ranged from 4.8-10.8% across databases. The proportion of TIA was 3.1% in the pooled dataset and ranged from 2.0-5.2% across databases.

The proportion of patients with severe or end-stage renal disease was <5% but the proportion of patients with mild (pooled 45.1%, database range 37.9-48.5%) or moderate (pooled 20.9%, database range 11.6-32.1%) renal impairment was high.

The prevalence of hepatic impairment, narrow-angle glaucoma and urinary retention and/or bladder outflow obstruction was not higher than 6%. The prevalence of benign prostatic hyperplasia (BPH) was much higher (pooled 13.8%) with high proportions in HSD and SIDIAP (14.7 and 19.2% respectively) where males accounted for approximately 2/3 of the study population.

For those databases where information on dosing was available (THIN, IPCI, HSD) NVA237 was prescribed according to the label (i.e., once daily) in more than 98% of first-time NVA237 users.

Off-label-use was assessed with respect to diagnostic indication and age. The indication of use for the majority of study patients was either "COPD" (pooled 75.0%, database range 68.0-88.6%) or "COPD and asthma" (pooled 8.3%, database range 2.3-22.7%), however large variations across databases were observed. Of the remaining treatment episodes, NVA237 was either prescribed for asthma (pooled 8.3%, range 3.0-10.1%) or prescribed for other indications (pooled 6.2%, database range 2.0-8.3%), resulting in a potential off-label use of 14.5% with respect to indication. The respective disease codes for those patients that received NVA237 for reasons other than COPD and/or asthma were reviewed, and in the majority of cases, NVA237 was initiated for reasons of respiratory symptoms or lower respiratory tract infections. NVA237 was prescribed to nine (<0.1%) patients below 18 years of age.

NVA237 was not prescribed to pregnant or lactating women. Use of other respiratory medications was high with country-specific differences observed for short-acting and long-acting bronchodilators being prescribed.

Discussion

During the study period we identified 13,707 incident users of NVA237, of which 1,261 (9.2%) had used NVA237 for a consecutive period of more than one year. The NVA237 users were comparable in terms of age and underlying cardiovascular co-morbidity across the databases. The majority of patients had moderate or severe COPD based on spirometry data. The proportion of off-label use with respect to indication of use (i.e. not for COPD) was 14.5%, however, mainly reflects inconsistency of disease coding (NVA237 prescribed for respiratory symptoms or worsening of symptoms because of LRTI). Off-label use with respect to use in patients younger than 18 years was low. Prescription of NVA237 to patients with high risk treatment conditions (i.e. patients with severe renal impairment, liver impairment, narrow angle glaucoma, urinary retention, unstable ischemic heart disease and severe cardiac ventricular arrhythmia) was low but underlying cerebrovascular and cardiovascular comorbidities were considerable. NVA237 was not prescribed to pregnant or lactating women.

Conclusion

Results presented in this final study report show that the majority of first-time prescriptions for NVA237 was in line with the product label with regard to dosing, indication of use and age. The proportion of NVA237 patients having high risk treatment conditions was low (i.e., patients with severe renal impairment, liver impairment, narrow-angle glaucoma, urinary retention, unstable ischemic heart disease and severe cardiac ventricular arrhythmia). Although proportions of study patients with underlying cerebro-cardiovascular comorbidities and mild-to-moderate renal impairment were relatively higher, these proportions seem to be in

line with reported prevalence estimates for the COPD population, as found in the published literature.

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2 List of abbreviations

ADM	Administrative
(A)MI	(Acute) Myocardial Infarction
ATC	Anatomical Therapeutic chemical Classification system
AV	Atrioventricular
BNF	British National Formulary
BPH	Benign prostatic hyperplasia
CHMP	Committee for Medicinal Products for human use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
DUS	Drug Utilization Study
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
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
IPCI	Integrated Primary Care Information Project
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene Receptor Antagonist
LRTI	Lower Respiratory Tract Infection
MR	Medical Record
NOS	Not otherwise specified
OTC	Over-the-counter
PASS	Post Authorization Safety Study
PDE	Phosphodiesterase
PSUR	Periodic Safety Update Report
RCT	Randomized Controlled Trial
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
TIA	Transient Ischemic Attack
THIN	The Health Improvement Network
UK	United Kingdom
UMLS	Unified Medical Language System
WHO	World Health Organization

3 Investigators

Project lead

Principal investigators (PI)

Sub-investigators

4 Other responsible parties

Marketing authorization holder contact person

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Scientific advisory committee (SAC)

[redacted]

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 November 2012	01 November 2012	None
End of data collection* for 1st interim report	Q4 2013	14 October 2013	None
Study progress report 1	25 October 2013	25 October 2013	None
End of data collection* for second interim report	Q3 2014	11 August 2014	None
Study progress report 2	07 October 2014	07 October 2014	None
End of data collection* for final report	Q4 2015	29 February 2016	None
Final report	Q2 2016	28 April 2016	None
Date of study registration in the EU PAS Register	26 September 2013	26 September 2013	None

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

6 Rationale and background

According to the 'Global initiative of lung disease' (GOLD), 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 to noxious particles or gases in the airways and the lungs (GOLD 2016). Exacerbations and co-morbidities contribute to the overall severity in individual patients. COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment (Pauwels et al 2001). COPD is a frequent disease, in Europe the COPD prevalence ranges from 4-10% in the adult population (Halbert et al 2006).

Bronchodilators are the mainstay of symptomatic management of COPD and include β2 agonists, anticholinergics, methylxanthines and phosphodiesterase-4 (PDE-4) inhibitors, used alone or in combination (GOLD 2016).

Use of inhaled long-acting muscarinic antagonists (LAMA) has been associated with an increased risk of anticholinergic effects such as glaucoma and urinary retention (Afonso et al 2011, Verhamme et al 2008). More recently, the use of LAMA has been suggested to be associated with an increased risk of cardiovascular and cerebrovascular events but the data are conflicting (Dong Yaa-Hui 2012, Jara et al 2007, Jara et al 2012, Lee et al 2008, Michele et al 2010, Singh et al 2011, Singh et al 2008, Verhamme et al 2012, Verhamme et al 2013, Wise et al 2013).

NVA237 is a synthetic, quaternary ammonium, anticholinergic (anti-muscarinic) agent that acts through competitive antagonism of acetylcholine at the muscarinic receptors. Seebri Breezhaler (along with the Multiple Marketing Authorizations Enurev Breezhaler and Tovanor Breezhaler) is the Novartis brand name for this LAMA. NVA237 is a dry powder formulation, developed as a once-daily inhalation treatment for patients with COPD. NVA237 is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients (aged 18 years or older) with COPD.

The recommended dose of Seebri Breezhaler is the inhalation of the content of one capsule once daily using Seebri Breezhaler. Each delivered dose of Seebri Breezhaler contains 55 micrograms of NVA237 equivalent to 44 micrograms of glycopyrronium. The recommended dose is the inhalation of the content of one capsule once daily using the Breezhaler inhaler.

The Summary of Product Characteristics (SmPC) of NVA237 specifies that the product should be used with caution in patients with a medical history of urinary retention and narrow-angle glaucoma, as these conditions could aggravate upon concomitant use of medications with anticholinergic effects. As NVA237 is predominantly cleared by the kidney, caution is needed when administered to patients with severe renal impairment or end-stage renal disease. Finally, as patients with a medical history of cardiovascular disease were excluded from the phase II - phase III clinical trials, NVA237 should be used with caution in these patients groups. Because such populations were not studied during a pre-marketing setting, the 'missing information' section of the Risk Management Plan (RMP) includes the following populations of interest: Use of NVA237 in patients with unstable ischemic heart disease, arrhythmia and long QT-syndrome; Use in patients with liver impairment; Use in pregnancy and lactation; Long-term use in COPD beyond one year; Off-label use in adults

with asthma without COPD and in the pediatric population; and the Safety and efficacy of alternative dosing regimens.

In the context of the NVA237 marketing authorization application and the multiple marketing authorization applications for Tovanor Breezhaler and Enurev Breezhaler, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to conduct a drug utilization study (DUS) to estimate the subpopulation with cardiovascular co-morbidity and to identify patients groups with missing information in the RMP. This DUS attempted to assess whether NVA237 is prescribed according to the current labeling. Results from the final analysis of this DUS are presented in this study report.

7 Research question and objectives

7.1 Main objectives

1. To determine the proportion of patients using NVA237 with the following cardiovascular or cerebrovascular co-morbidities:
   - Cardiovascular diseases: unstable ischemic heart disease, heart failure, myocardial infarction, cardiac arrhythmia (atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and "Torsade de pointes"), long QT syndrome and atrioventricular (AV) block)
   - Cerebrovascular diseases: hemorrhagic or ischemic stroke, transient ischemic attack (TIA)
2. To determine the proportion of patients using NVA237 who have underlying conditions corresponding to the population defined in the 'Missing information section' of the RMP or who have high risk treatment conditions:

   2a) To determine the proportion of patients using NVA237 with a history of the following conditions:
   - Unstable ischemic heart disease, cardiac arrhythmia and long QT-syndrome
   - Urinary retention or symptomatic bladder outflow obstruction
   - Narrow-angle glaucoma
   - Renal impairment
   - Liver disease
   - Pregnancy or breast feeding (at the moment of initiating NVA237 and during the first NVA237 treatment episode)

   2b) To determine the proportion of patients using NVA237 who do not meet the criteria specified in the NVA237 label (i.e., proportion of patients with 'off-label use' i.e., use of NVA237 in patients younger than 18 years or in patients without a diagnosis of COPD.

   2c) To determine the proportion of new initiators of NVA237 with an uninterrupted use for more than one year.

7.2 Secondary objectives

To describe the patient characteristics of new initiators of NVA237 in terms of:

- Demographics (age and gender)
- COPD duration (from diagnosis of COPD until first prescription of NVA237)
- COPD exacerbation (need of oral corticosteroids and/or hospitalization for COPD) in one year prior to first prescription of NVA237)
- COPD severity
- Smoking status at time of first prescription of NVA237
- Prescribed dosage/posology
- Concomitant use of other respiratory medications
- Concomitant use of other anticholinergic medications

8 Amendments and updates to the protocol

Table 8-1 Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
1	17 June 2013	4. Abstract	The abstract has been updated clarifying the study size, the rationale and background and the primary/secondary objectives of this study.	Based on PRAC comments
2	17 June 2013	7. Rationale and background	This section has been updated clarifying that this DUS will be conducted to estimate the subpopulation of NVA237 users with cardiovascular co-morbidity and to identify patient groups with missing information in the risk management plan.	Based on PRAC comments
3	17 June 2013	8. Research question and objectives	The objectives have been updated. The primary objective of this study is to determine the proportion of patients using NVA237 who also have cardio/cerebrovascular comorbidities and to identify patient groups with missing information in the risk management plan.	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
4	17 June 2013	9.2.2 Study period	Study period has been clarified stating that 3000 patients will be included within 3 years after launch (= November 2015).	Based on PRAC comments
5	17 June 2013	9.3.7 Underlying comorbidity	This section has been updated. Arrhythmia is one of the comorbidities of interest and encompasses: atrial fibrillation/flutter, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”), long QT syndrome and AV block.	Based on PRAC comments
6	17 June 2013	9.4 Data sources	Details on the methods for collection of hospitalization data have been added.	Based on PRAC comments
7	17 June 2013	9.5 Study Size	The sample size of 3000 patients, to be enrolled within 3 years after launch, has been clarified. This session now also contains information on population coverage of the individual databases and the projected market uptake of NVA237.	Based on PRAC comments
8	17 June 2013	9.6 Data management	This section has been updated with information on the methods that will be used to pool the data of the different databases.	Based on PRAC comments
9	17 June 2013	Annex 2 – Indication of use and co-morbidity definition	The codes for the co-morbidities for “cardiovascular diseases” presented in Annex 2 have been expanded to also include “ischemic heart disease”	Based on PRAC comments
10	05 September 2014	Secondary objective	Now also includes COPD disease severity measured by proxy or by pulmonary function	To provide better insight into COPD severity in patients initiating NVA237

Number	Date	Section of study protocol	Amendment or update	Reason
11	05 September 2014	9.3.3 Indication of use for inhaled NVA237	In case NVA237 is prescribed for other reasons than COPD or asthma, the respective disease codes, around the prescribing of NVA237 will be provided	Internal request by Novartis
12	05 September 2014	9.3.7 Underlying co-morbidities	Cardiac arrhythmia as comorbidity has been updated and now also includes supraventricular tachycardia, sick sinus syndrome and premature depolarization	Based on SAC comment
13	05 September 2014	9.3.7 Underlying co-morbidities	BPH has been added as comorbidity	Based on SAC comment
14	05 September 2014	Annex 4 - Indication of use and co-morbidity definition	Disease codes have been updated	Based on continuous review of disease codes
15	05 September 2014	Annex 3 - Exposure and concomitant medication definition	Drug codes have been updated	Based on continuous review of disease codes
16	05 September 2014	9.5 Study size	Clarification and justification of study sample size; clarification of discontinuation rule based on accrued no. of patients and duration of follow-up	Justification of sample size based on previous response already submitted to PRAC in 2013, but details not yet in protocol; discontinuation rule based on patient counts identified during current preparation of second yearly interim report
17	05 September 2014	Not applicable	Transcription of the entire protocol into the Novartis protocol template for non-interventional PASS	To follow Novartis-internal guidelines

9 Research methods

9.1 Study design

This was a multinational, multi-database cohort study using five electronic health care databases from various European countries, namely The Netherlands (NL), Italy (IT), United

Kingdom (UK), Denmark (DK), and Spain (ES) (for database details, see Section 9.5 - Data sources and measurement and Annex 2.7 - Data sources). As NVA237 was not introduced at the same time in all participating countries (see Table 9-1), there were 28 months of available data for selection of new NVA237 users in UK (THIN), 26 months in Denmark (Aarhus), 25 months in The Netherlands (IPCI) and 21 months in Spain (SIDIAP) and Italy (HSD).

Over the past three years, new users of NVA237 were selected within the respective database updates. It should be noted that patients selected for inclusion in the first interim analysis may have been excluded from the second or third interim analyses in cases where General Practitioners (GPs) decided to discontinue contribution of patient data to the respective database or if practices changed IT software and the minimum requirement of one year of database history was re-set.

For this final report we selected a cohort of patients newly treated with NVA237. Patient characteristics were assessed either at time of first NVA237 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 Netherlands [NL], Italy [IT], United Kingdom [UK], Denmark [DK] and Spain [ES]). This final study report presents results for 28 months of data accrual, namely from 01 November 2012 to 01 March 2015. Based on availability of database-specific updates, THIN data were used from 01 November 2012 to 01 March 2015, Aarhus from 01 November 2012 to 31 December 2014, IPCI from 01 February 2013 to 01 March 2015, and both HSD and SIDIAP from 01 April 2013 to 31 December 2014.

For more detailed information on the individual databases, see Section 9.5 - Data sources and measurement and Annex 2.7 - Data sources.

This study was planned to cover patient data from first launch of NVA237 in any of the participating countries (November 2012) up to a maximum of 3 years following this first launch. The number of patients accrued in the study was assessed yearly when preparing the interim reports. The study has now been discontinued, as the number of patients with at least one year of follow-up exceeded 3,000.

The launch dates of NVA237 in the countries of the databases are shown below in Table 9-1.

Table 9-1 Launch dates for NVA237 in the five participating countries

Country	Actual launch date
Denmark	26 November 2012
Italy	15 April 2013
Netherlands	01 February 2013
Spain	15 April 2013
United Kingdom	02 November 2012

9.3 Subjects

9.3.1 In- and exclusion criteria

From the databases containing available NVA237-exposure data from November 2012 onwards, a cohort of patients with a first-time prescription or dispensation of NVA237 was selected.

Patients without one year of database history before the first prescription of NVA237 were excluded from the study. No further exclusion criteria were applied.

9.3.2 Follow-up

Patients initiating NVA237 were followed from time of the first prescription until the earliest of (i) end of treatment, (ii) end of data collection for the final analysis, (iii) disenrollment from the database or (iv) death.

9.4 Variables

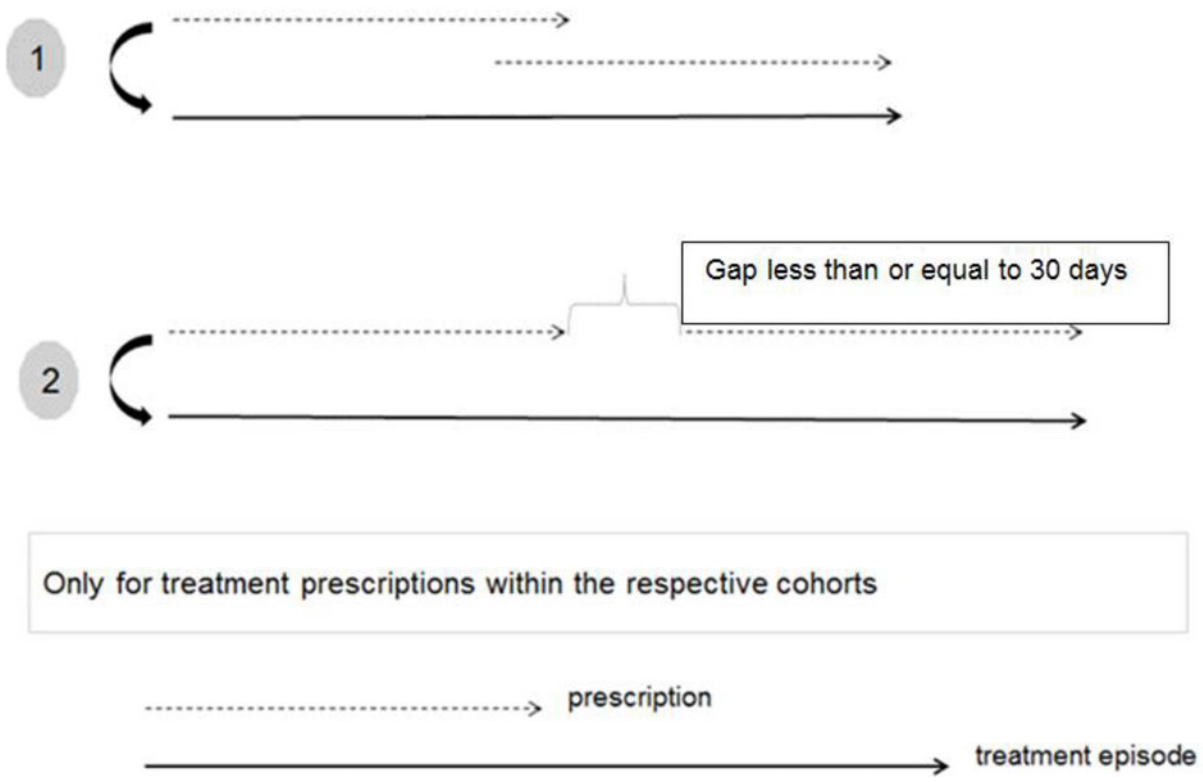
9.4.1 NVA237-exposure and duration of use

Patients prescribed NVA237 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 medication (i.e., 50 µg once daily for NVA237 or other respiratory medications/drug classes of interest [for the assessment of concomitant use of other respiratory medications]). 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 NVA237



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

- For all patients, information on gender and age (at time of first prescription of NVA237) was captured
- If available, information on smoking status was retrieved; patients were classified as "current smoker", "past smoker", "non-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 of NVA237)
- Number of COPD exacerbations requiring hospitalization 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), or using a combination of COPD codes (see Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of NVA237, and codes for COPD exacerbation as indication of use of systemic corticosteroids and antibiotics) with information from hospital referral and discharge letters (IPCI) or using a combination of disease codes with source codes (hospital discharge letters) (THIN)

- COPD severity at time of first prescription of NVA237 (see Annex 2.4 – COPD definition)
- 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 one month before and one week after AB prescription date) of prescription of the AB in order to determine if the prescription data were able to be used in this analysis.

9.4.3 Indication of use of inhaled NVA237

For each patient initiating treatment with NVA237 the indication of use was assessed. Indication of use was classified as follows:

- COPD
- COPD and asthma
- Asthma (without COPD)
- Other (neither COPD nor asthma recorded in database)
- Unknown (patients for whom there are no disease codes entered at the time of the NVA237 prescription (maximum +/- one month of prescription date)

The indication of use was identified in the databases based on disease-specific codes (see Annex 2.2, Annex 2.4, and Annex 2.5).

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 NVA237-use, the complete medical record of the patient was considered. However, asthma as indication for NVA237-use was only considered if the recorded date of asthma fell within a maximum period of one year prior to the index date. If NVA237 was prescribed for reasons other than COPD or asthma, the respective respiratory disease codes were provided.

Potential off-label use of NVA237 was defined as an indication of use not including a COPD diagnosis. NVA237 prescribed/dispensed to patients having a diagnosis of both COPD and asthma was not considered off-label use, as per protocol. Patients for which no indication could be identified (unknown) were not counted as off-label users.

9.4.4 Prescribed dosage/posology

Each delivered dose of NVA237 contains 55 micrograms of glycopyrronium bromide equivalent to 44 micrograms of glycopyrronium. The recommended dose is the inhalation of the content of one capsule once daily using the Breezhaler® inhaler.

Although it is expected that patients use NVA237 once daily, the frequency of use in this study was assessed as follows, based on the patient-specific dosing regimen (if available):

- Once daily
- Every other day
- Twice daily

- 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 Concomitant use of other respiratory medications

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

- Short acting muscarinic antagonists (SAMA)
- LAMA (other than NVA237)
- Single-ingredient short acting β_2 agonists (SABA)
- Single-ingredient inhaled long acting β_2 agonists (LABAs
- Inhaled corticosteroids (ICS)
- Xanthines
- Fixed combination therapy (LABA + ICS, anticholinergic agents + SABA, LABA+LAMA)
- Oral $ß_2$-agonists
- Leukotriene receptor antagonists (LTRA)
- Systemic corticosteroids
- Oral phosphodiesterase-4 (PDE-4) inhibitors

9.4.6 Concomitant use of systemic anticholinergic medications

Information on the concomitant use of other anticholinergic medications was retrieved from the prescription records and was assessed in the six months prior to the index date (including medications initiated at index date). These medications were retrieved via an automated search for either ATC or Multilex codes (see Annex 2.6). The following types of medications were considered as anticholinergic medications:

- Antipsychotic medications
- 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

9.4.7 Underlying co-morbidities

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

Co-morbidities of interest were the following:

- Chronic kidney disease (CKD) (with relevant stages)
- Narrow-angle glaucoma
- Urinary retention or symptomatic bladder outflow obstruction
- Benign prostatic hyperplasia (BPH)
- Cardiovascular disease including
  a. - unstable ischemic heart disease (= unstable angina pectoris and myocardial infarction)
  b. - heart failure,
  c. - myocardial infarction
  d. - cardiac arrhythmia (atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and "Torsade de pointes"), long QT syndrome and atrioventricular (AV) block, supraventricular tachycardia, sick sinus syndrome and premature depolarization)
- 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 CKD or via the estimated glomerular filtration rate (eGFR) if serum creatinine levels were available (all databases) (Levey et al 2009).

9.4.8 Pregnancy or breastfeeding at initiation of NVA237

Information on breastfeeding at initiation of NVA237 was available in THIN, IPCI and SIDIAP where it is captured using specific codes or free text; these are not available for HSD. Codes for pregnancy and/or breastfeeding are described under item 14 of Annex 2.2. In Aarhus, information on pregnancy was available via linkage with the Danish birth register.

Pregnancy was determined at or during 9 months prior to the index date and during exposure to NVA237 (first treatment episode only). Lactation was determined at or during 12 months prior to the index date and during exposure to NVA237 (first treatment episode only).

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 medications, 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 NVA237. 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 and have been validated for pharmacoepidemiologic research (Cazzola et al 2011, Ehrenstein et al 2010, Garcia-Gil Mdel et al 2011, Lewis et al 2007, Vlug et al 1999).

The databases being used for this study are THIN (UK), HSD (IT), IPCI (NL), the Aarhus University Prescription Database (DK), and SIDIAP (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. The primary care databases represent 3.0-13.0% of the country-specific total population. As of 2015, the total number of active persons in the source population encompassing all five databases was 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, *millions*	1.6	3.8	1.4	1.1	5.6
Mean follow-up in the database (years)	3.3	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	Twice per year (January/July)	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 medications	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes

Database characteristics	IPCI	THIN	Aarhus	HSD	SIDIAP
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

Data-cuts used for this final report are based on new-user exposure to NVA237 and availability of database-specific updates as follows: IPCI from 01 November 2012 to 01 March 2015, THIN from 01 November 2012 to 01 March 2015, Aarhus from 01 November 2012 to 31 December 2014, HSD from (01 November 2012 to 31 December 2014) and SIDIAP (01 November 2012 to 31 December 2014)

Further information on the participating databases can be found in Annex 2.7 – Data sources.

9.6 Bias

As this is a DUS, the issue of potential bias is less of a concern. There is the potential for diagnostic bias, as co-morbidity was assessed via disease-specific codes. If disease coding is inconsistent or differential, this could result in diagnostic bias. Validation studies have shown that coding is reliable in these databases and that they are suitable for pharmacoepidemiologic research (Cazzola et al 2011, Ehrenstein et al 2010, Garcia-Gil Mdel et al 2011, Lewis et al 2007, Vlug et al 1999). For this study, indication of use of NVA237 is important. However, indication of use might be incomplete or missing as in Aarhus. If indication of use was missing from the prescription files, the medical file was searched for disease codes at the time of NVA237 prescription (maximum +/- 1 month of prescription 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 smoking status might be missing or reported inconsistently. Further sources of bias and their potential effects on study results are discussed in Section 11.2 – Limitations.

9.7 Study size

This DUS was an exploratory, descriptive study. The study size consisted of the sum of new initiators of NVA237 derived from each database, excluding those who were not eligible according to the exclusion criteria. As no hypothesis was tested and prediction of market uptake of a new product was difficult, it was decided to include a total of 3,000 patients initiating NVA237 (including all databases) within 3 years of product launch.

Two-sided 95% confidence intervals (CIs) for co-morbidities of interest, which are based on background prevalence data found in the medical literature, are listed in the table below. The CIs were estimated using the exact (Clopper-Pearson) method. This estimation was based on the proposed sample size of 3,000 patients.

Table 9-3 Estimated two-sided 95% CIs for co-morbidities of interest (N=3,000)

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

Source: *Conservative estimates of background prevalence were used 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 on this estimation, a sample size of 3,000 patients produces a two-sided 95% CI of 3.51-4.98 when the background prevalence is 4.2 (n=126). Similarly, a sample size of 3,000 patients produces a two-sided 95% CI of 12.20-14.67 when the background prevalence is 13.4 (n=402) (see Table 9-3 for details). Therefore, Novartis believes that the proposed sample size of 3,000 patients is sufficient to describe the use of NVA237 in patients with different cardiovascular or other co-morbidities (including missing information). The actual study size was affected by market uptake of NVA237 in the countries of interest. The number of patients accrued in the study was assessed yearly during preparation of interim reports. The study was discontinued because the number of patients with at least one year of follow-up exceeded 3,000.

9.8 Data transformation

This final study report describes data from five different databases (Aarhus, IPCI, THIN, HSD and SIDIAP). Data were extracted, validated and cleaned locally. There is no uniform coding scheme across all participating databases (e.g., ICD9-CM (HSD) and ICD-10 (Aarhus, SIDIAP), ICPC (IPCI), READ (THIN)), and 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/co-morbidity, a medical definition was created and, based on such definition; relevant UMLS concepts were identified and projected into the database-specific terminologies.

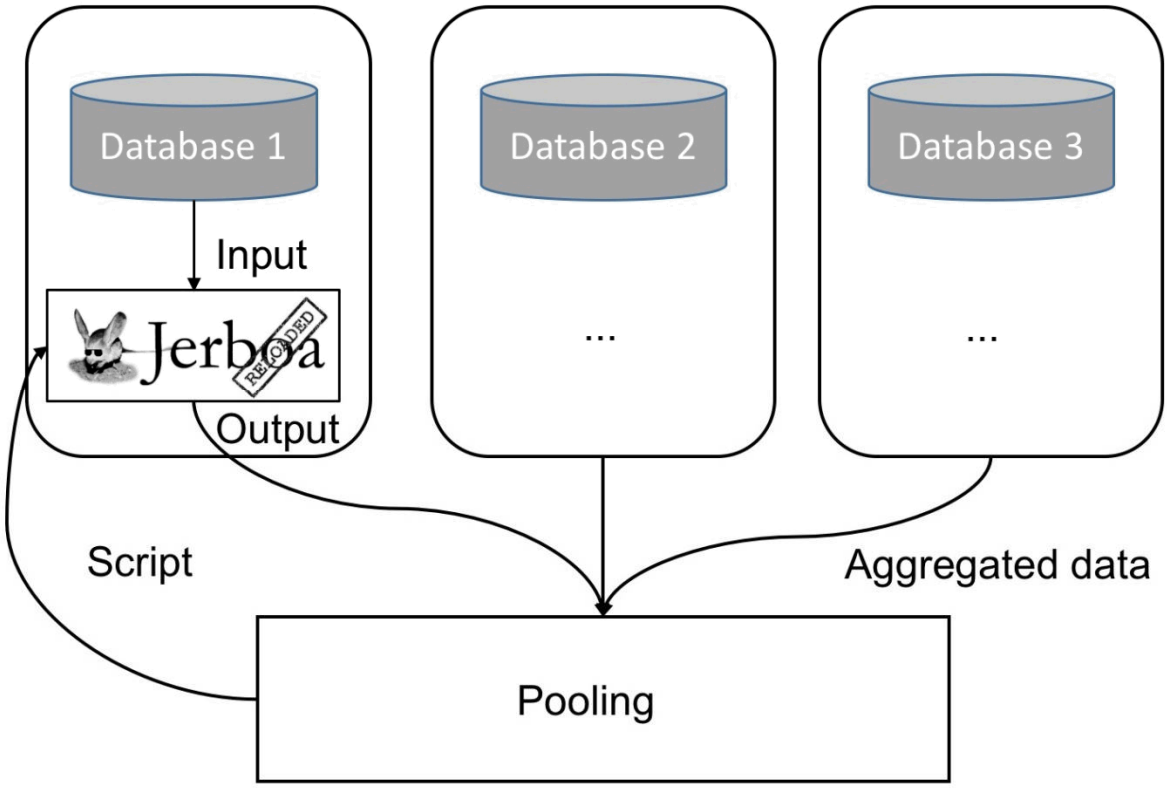
2. Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm was constructed for each co-morbidity 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, medication, 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 9-2). 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 9-2 Model for data sharing and elaboration



Source: www.EU-ADR-project.org

4. Benchmarking of disease prevalence rates

For each co-morbidity of interest, we benchmarked database-specific prevalence rates using Jerboa. The observed prevalence rates were compared 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 NVA237 exposure cohorts
- Indication of use and dosing of NVA237
- Duration of NVA237 use, proportion of patients with an uninterrupted use for more than one year
- Baseline characteristics in terms of demography, life style factors and COPD characteristics at or prior to first NVA237 prescription
- Baseline characteristics in terms of co-morbidity and concomitant medication use at or prior to first NVA237 prescription

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

Off-label use is presented separately to age and indication. The proportion of patients with a potential off-label indication was calculated as the number of patients with an indication other than COPD or COPD and asthma divided by the overall number of NVA237 initiators for whom information on indication of use was available.

9.9.2 Main statistical methods

Categorical data are presented as counts (n) and proportions (%) with 95% CIs. 95% CIs were calculated using the Wilson method. For continuous data, the number of observations (n), mean, SD, and median (with minimum and maximum values) are presented.

Data were analyzed by database and overall (pooled-database analysis). Additionally, an analysis by calendar year was performed to evaluate trends over time.

9.9.3 Missing values

No imputation of missing values was carried out. Missing values are represented in separate categories. In- or exclusion of the number of missing values in the denominator was applied depending on the relevance for each characteristic. Missing values were excluded from the denominator to calculate off-label use based on indication of use, to calculate COPD severity and to calculate smoking status.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

The study was conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (ISPE 2008) and according to the ENCePP code of conduct (ENCePP 2014).

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

10.1 Participants

The individual study periods for the respective databases are presented in Table 10-1. These study periods are based on the most recent database-specific updates. The overall study period was from 01 November 2012 to 01 March 2015.

In total, more than 13.5 million eligible patients were identified during the study period. Eligible patients were those 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	01 Nov 2012 to 01 Mar 2015	01 Nov 2012 to 01 Mar 2015	01 Nov 2012 to 31 Dec 2014	01 Nov 2012 to 31 Dec 2014	01 Nov 2012 to 31 Dec 2014
Number of eligible patients during study period	3,851,828	1,661,470	1,426,372	1,111,850	5,635,949

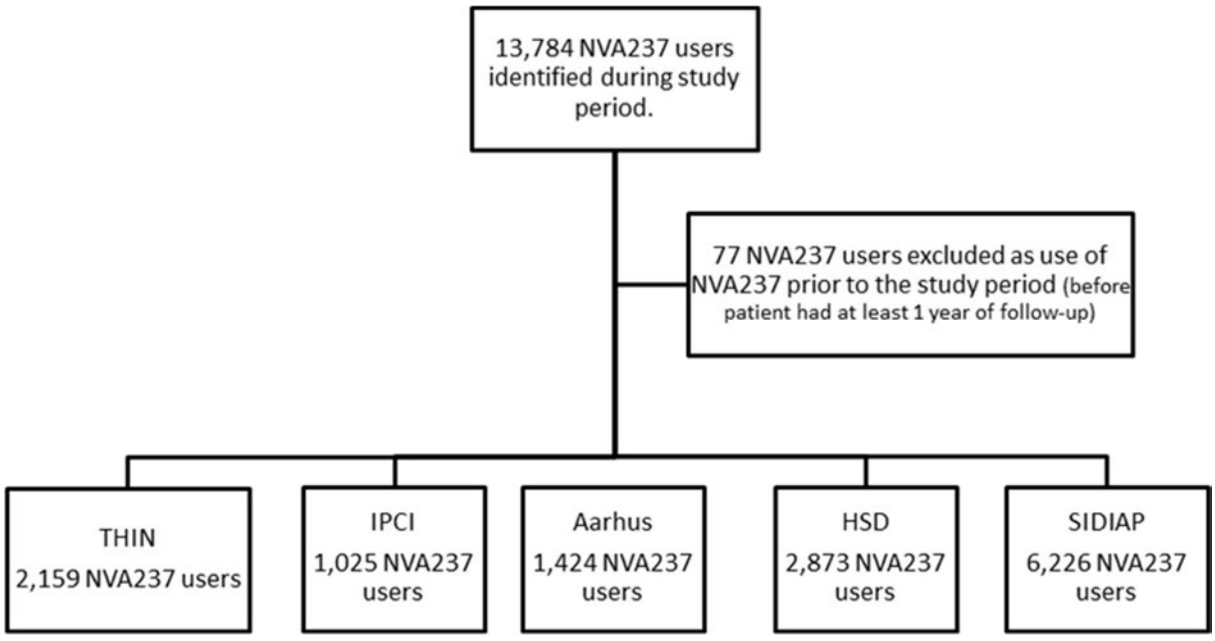
*based on the THIN mid-year count in 2014; **based on subset of patients in the database for whom lung function data are available (i.e., FEV1) and optimal linkage to hospital & out-patient registers exist; ***based on active patients in the database (of note: previous interim reports presented eligible patient numbers for HSD that were not limited to active patients only)

10.2 Descriptive data

10.2.1 Baseline characteristics of NVA237 users

Across all five databases, 13,784 NVA237 initiators were identified, of which 77 were excluded as not having one year of valid database history before their first NVA237-prescription. The breakdown of excluded patients by database is: 56 from IPCI (Nl), 13 from THIN (UK), six from SIDIAP (ES), one from HSD (IT), and one from Aarhus (DK) (see Figure 10-1).

Figure 10-1 Patient selection flowchart



In total, 13,707 incident users of NVA237 remained in the study cohort: 2,159 in THIN, 1,025 in IPCI, 1,424 in Aarhus, 2,873 in HSD and 6,226 in SIDIAP. Baseline characteristics of NVA237 users are shown in Table 10-2 below. Based on pooled data the median age at time of NVA237 initiation was 71 years, and 208 patients (1.5%) were under 40 years of age at the time of first NVA237 prescription. Of these, nine were below the age of 18 (0.1%). A total of 5,952 patients (43.4%) had at least one year of follow-up after NVA237 initiation. The proportion of patients with at least one year of follow-up was lowest for HSD (34.6%) and highest for Aarhus (60.8%).This relatively higher proportion for Aarhus could have resulted because (1) launch of NVA237 in Denmark was approximately five months earlier than in Italy and (2) the population in Aarhus is less dynamic since it is a collection of regional databases.

Overall, NVA237 was prescribed more frequently to men (59.9%) than women. The proportion of men varied between databases and was highest in SIDIAP (67.6 [95% CI 66.4-68.8%]) and lowest in THIN (49.2 [95% CI: 47.1-51.3%]).

Among patients for whom information on smoking status was available (87.0% of the pooled study population), approximately one third of NVA237 initiators were current smokers, 27.9% were non-smokers, and 42.4% were past-smokers. The proportion of current smokers ranged from 23.3-37.9% and the proportion of past-smokers ranged from 34.9-53.7%. Largest differences between databases were observed for non-smokers with proportions of 30.0% and 37.0% for HSD and SIDIAP, respectively, and a much lower range for the other databases (8.9-14.8%) (see appendices, Figure 16-1).

Baseline characteristics of the database-pooled study population by calendar year are presented in the appendices (see Table 16-1). The majority of NVA237 initiators (98.7%) ‘entered’ the study in 2013 and 2014. Differences in gender distribution and smoking status were observed for 2012 and 2015 versus 2013 and 2014.

Table 10-2 Characteristics of the study cohort, by database and pooled

Characteristic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Gender												
Female	1,097 (50.81)	48.70-52.92	478 (46.63)	43.60-49.70	696 (48.88)	46.29-51.47	1,209 (42.08)	40.29-43.90	2,017 (32.40)	31.25-33.57	5,497 (40.10)	39.29-40.93
Male	1,062 (49.19)	47.08-51.30	547 (53.37)	50.30-56.40	728 (51.12)	48.53-53.71	1,664 (57.92)	56.10-59.71	4,209 (67.60)	66.43-68.75	8,210 (59.90)	59.07-60.71
Age												
Mean (SD)	69.65 (11.11)		67.91 (11.75)		69.13 (10.33)		71.97 (11.74)		69.61 (12.29)		69.94 (11.81)	
Median (IQ range)	69.96 (62.33-77.75)		68.61 (60.65-76.83)		69.14 (62.37-76.46)		73.68 (65.87-80.29)		70.72 (62.42-78.81)		70.98 (62.88-78.66)	
Min-max	17.75-102.06		16.51-96.19		40.35-96.13		17.61-95.7		10.11-100.36		10.10-102.05	
Age category												
<18	1 (0.05)	0.01-0.26	1 (0.10)	0.02-0.55	0 (0.00)	0.00-0.27	1 (0.03)	0.01-0.20	6 (0.10)	0.04-0.21	9 (0.07)	0.03-0.12
18 < 40	10 (0.46)	0.25-0.85	12 (1.17)	0.67-2.04	0 (0.00)	0.00-0.27	51 (1.78)	1.35-2.33	126 (2.02)	1.70-2.40	199 (1.45)	1.26-1.67
40 < 60	413 (19.13)	17.53-20.84	224 (21.85)	19.43-24.49	278 (19.52)	17.55-21.66	362 (12.60)	11.44-13.86	1,115 (17.91)	16.98-18.88	2,392 (17.45)	16.82-18.10
60 - 80	1,327 (61.46)	59.39-63.49	634 (61.85)	58.84-64.78	917 (64.40)	61.87-66.84	1,710 (59.52)	57.71-61.30	3,667 (58.90)	57.67-60.11	8,255 (60.22)	59.40-61.04
> 80	408 (18.90)	17.30-20.60	154 (15.02)	12.97-17.34	229 (16.08)	14.27-18.08	749 (26.07)	24.50-27.71	1312 (21.07)	20.08-22.10	2,852 (20.81)	20.14-21.49
Smoking status (assessed at index date)*												
Missing	2 (0.09)	0.03-0.34	117 (11.41)	9.61-13.51	781 (54.85)	52.25-57.41	609 (21.20)	19.74-22.73	266 (4.27)	3.80-4.80	1,775 (12.95)	12.40-13.52

Characteristic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Current smoker	768 (35.61)	33.61-37.65	344 (37.89)	34.79-41.09	241 (37.48)	33.82-41.29	795 (35.11)	33.18-37.10	1,391 (23.34)	22.28-24.43	3,539 (29.66)	28.85-30.49
Past smoker	1,133 (52.53)	50.42-54.63	430 (47.36)	44.13-50.61	345 (53.65)	49.79-57.48	790 (34.89)	32.96-36.88	2,366 (39.70)	38.46-40.95	5,064 (42.44%)	41.56-43.33
Non-smoker	256 (11.87)	10.57-13.30	134 (14.76)	12.60-17.21	57 (8.86)	6.91-11.31	679 (29.99)	28.14-31.91	2,203 (36.96)	35.75-38.20	3,329 (27.90%)	27.10-28.71
Number of patients with at least 1 year of follow-up since NVA237 start	907 (42.15)	40.08-44.25	493 (48.10)	45.05-51.16	866 (60.81)	58.25-63.32	993 (34.56)	32.85-36.32	2,693 (43.25)	42.03-44.49	5,952 (43.42)	42.6-44.25

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

10.2.2 COPD characteristics of patients initiating NVA237

COPD characteristics were assessed during the year prior to initiation of NVA237 and are presented in detail in the appendices (see Table 16-2). To assess COPD severity, the most recent spirometry data (where available) up to a maximum of five years prior to NVA237-initiation were used.

The pooled median duration of COPD was 5.3 years with the shortest median duration for Aarhus (4.3 years) and the longest median duration for IPCI (5.8 years). The number of patients identified with COPD exacerbations requiring hospitalization was low – less than 5% of patients had been hospitalized at least once in the year prior to index date. The pooled proportion of use of systemic corticosteroids for treatment of COPD exacerbation in the year prior to index date was 12.9% however large variations were observed across databases with a proportion of only 4.0% for SIDIAP and almost 30% 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 14.5% (Aarhus) to 51.1% (HSD), with pooled estimate of 26.5%.

Spirometry was available for THIN (81.9% of study patients), IPCI (35.8%), HSD (26.9%) and SIDIAP (48.8%). The number of patients assessed as not having COPD based on spirometry data was high (34.0% in pooled dataset). Only spirometry data up to five years prior to NVA237 initiation was considered for the assessment. For Aarhus, only FEV1-data were available for 28.0% of study patients; hence, assessment of COPD severity in the Aarhus study population was not possible. Based on the pooled data, 8.8% of patients had mild COPD, 48.9% moderate, 35.8% severe and 6.4% very severe. Comparing severity stages across databases, poportions of patients were generally similar, but with a few exceptions: Proportion of patients with mild COPD was somewhat higher in IPCI than in the other databases; proportion of patients in HSD with severe (26.7%) and very severe COPD (2.0%) were lower compared to the other databases (see Figure 16-2). 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 (54.9-89.1%, pooled 74.0%) or severe COPD (6.1-23.7%, pooled 14.0%) (see Figure 16-3).

10.2.3 Prescribed dosage and treatment duration of NVA237

Information on dosage was available for THIN, IPCI and HSD only. Prescribed dosage of NVA237 was “once daily” for >98.0% of these patients (see Table 10-3).

The pooled median duration of NVA237 was 61 days. When comparing databases, the median duration of use of NVA237 was similar between THIN, IPCI and Aarhus (85, 82 and 90.5 days respectively). The median duration of NVA237 use was lower in Spain (61 days) and Italy (48 days) which can be explained by the fact that NVA237 was only registered in these countries in April 2013 and treatment episodes were censored at the end of database collection (i.e., December 2014). This can also be observed in Table 16-3, where median duration of NVA237 decreases calendar year upon calendar year. Among the subset of patients who had at least one year of follow-up after NVA237-initiation, 1,261 (20.1%) used NVA237 without interruption for more than one year.

Table 10-3 Prescribed dosage of NVA237 assessed at index date, median duration of treatment, and uninterrupted use of NVA237 for more than 1 year, by database and pooled across databases

	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Prescribed dosage of NVA237 at index date												
Once daily*	2,113 (97.87)	97.17-98.40	977 (98.39)	97.4-99.01	n.a.	n.a.	2,830 (98.06)	97.49-98.5	n.a.	n.a.	5,920 (98.26)	97.89-98.56
Every other day*	43 (1.99)	1.48-2.67	0 (0.00)	0.00-0.39	n.a.	n.a.	0 (0.00)	0-0.13	n.a.	n.a.	43 (0.71)	0.53-0.96
Twice daily*	3 (0.14)	0.05-0.41	15 (1.51)	0.92-2.48	n.a.	n.a.	41 (1.42)	1.05-1.92	n.a.	n.a.	59 (0.98)	0.76-1.26
Other*	0 (0.00)	0.00-0.18	1 (0.10)	0.02-0.57	n.a.	n.a.	0 (0.00)	0-0.13	n.a.	n.a.	1 (0.02)	0-0.09
Dosage missing	n.a.	n.a.	32 (3.12)	2.22-4.37	1424 (100)	99.73-100	2 (0.07)	0.02-0.25	6,226 (100)	99.94-100	7,684 (56.06)	55.23-56.89
Median duration of NVA237 (days)(min-max)	85 (1-749)		82 (2-694)		90.5 (2-765)		48 (1-618)		61 (13-639)		61 (1-765)	
Number of patients who use NVA237 uninterruptedly for >1 year	285 (13.20)	11.84-14.69	101 (9.85)	8.18-11.83	237 (16.64)	14.80-18.67	141 (4.91)	4.18- 5.76	497 (7.98)	7.34- 8.68	1,261 (9.20)	8.73-9.70

*denominator=number of patients for whom information on dosage is available

10.2.4 Co-morbidity in patients initiating NVA237

Co-morbidity was assessed at index date and in the complete medical history of patients initiating NVA237 prior to index date; findings are presented in detail in the appendices (see Table 16-6, Table 16-7, Table 16-8, Table 16-9.

Those co-morbidities defined as main study objectives are described in Sections 10.4.1 and 10.4.2, and in Table 10-4.

10.2.5 Use of other medications in patients initiating NVA237

Respiratory medications

Use of other respiratory medications on or in the six months prior to index date is presented in detail in the appendices (see Table 16-10 and Figure 16-6). Use of short-acting bronchodilating medications, especially SABA, was high with a pooled proportion of 41.0% for SABA . Obvious differences were observed between databases. The use of short-acting β_2-agonists was higher in THIN (86.2%), IPCI (41.2%) and Aarhus (46.3%) than in SIDIAP (36.7%) and HSD (13.4%). Use of other short-acting agents such as SAMA or the combination of SAMA+SABA 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 (0.4%) and Spain (0.3%)).

In the pooled data, 20.1% of patients initiating NVA237 had been prescribed an ICS in the six months prior to index date with the highest proportions for Spain (20.3%) and Italy (28.5%).

With respect to the use of long-acting bronchodilating medications (LABA or LAMA), in the UK, the proportion of patients using LAMA (39.8%) was higher than LABA (12.2%), whereas the proportion of LABA and LAMA use was more comparable for the other databases. The fixed combination of LABA+ICS was frequently prescribed (database-pooled proportion 46.2%) with the highest proportion in the UK (59.1%) and the lowest proportion in Denmark (39.0%).

In the pooled population, 31.8% of patients received a systemic corticosteroid in the six months prior to index date, with the highest proportions in THIN (43.4%) and IPCI (42.2%). When considering use of systemic corticosteroids indicated for “COPD exacerbation” only, the pooled proportion was 10.4% (23.7% in IPCI, 17.8% in HSD, 16.8% in THIN, 8.9% in Aarhus, and 3.2% 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 (9.1%) and lowest proportion for Spain (2.1%) (database-pooled proportion 4.0%). Proportion of LTRA-use in the pooled population was 5%. Use of other respiratory medications such as oral β_2-agonists and PDE-4 inhibitors was low (<2%) in all databases.

Medications with anticholinergic effects

Amongst products with anticholinergic effects (see Table 16-11), mainly antidepressants (tricyclic and tetracyclic), H1-antihistaminics and antipsychotics were prescribed. Use of antidepressants in the pooled dataset was 9.1% (range 5.6-15.6%). Use of H1-antihistaminics

in the pooled dataset was 12.0% with the highest proportion in SIDIAP (15.0%) and the lowest proportion in Aarhus (5.0%). Use of antipsychotics was comparable across databases (range across databases from 2.1 to 5.5%, database-pooled estimate 4.4%).

Use of other product classes with anticholinergic effects, such as anticholinergics for overactive bladder, antispasmodics, disopyramide, antiparkinson medications, cholinesterase inhibitors and atropine, was low or non-existent.

10.3 Outcome data

Not applicable.

10.4 Main results

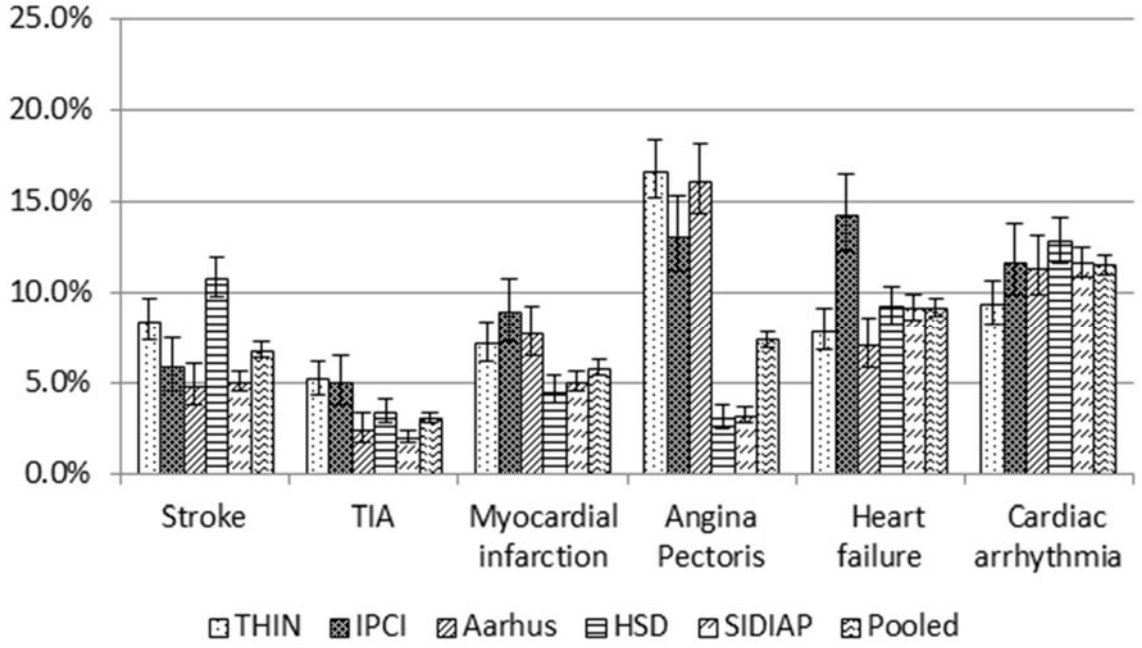
10.4.1 Cardiovascular and cerebrovascular comorbidities

In the pooled dataset, the proportion of patients with a history of cardiac arrhythmia (= a medical history of atrial flutter/fibrillation, AV-block, ventricular tachycardia/fibrillation or Long QTc/Torsade de Pointes) was 11.5% (ranging from 9.4-12.8% across databases). The proportion of heart failure in the pooled dataset was 9.1% and ranged from 7.1-14.2% across databases. The proportion of MI in the pooled dataset was 5.8% and 7.4% for angina pectoris. With regard to ischemic conditions, differences were observed between databases with especially lower proportions of angina pectoris in Italy (3.0%) and in Spain (3.2%) compared to the other databases (range 13.1-16.7%). The proportion of patients with unstable angina pectoris ranged from 0.6 to 3.3 % (pooled 1.3%). The number of patients with malignant ventricular arrhythmia was low, namely less than 0.5%.

The proportion of patients with a history of stroke was 6.8% in the pooled dataset and ranged from 4.8 to 10.8% per database. The proportion of TIA was 3.1% in the pooled dataset and ranged from 2.0-5.2% across databases.

Database-specific results for cardiovascular and cerebrovascular comorbidities are depicted in Figure 10-2 below and presented in detail in the appendices (see Table 16-6; by calendar year, see Table 16-7). The prevalences of the respective comorbidities of interest remained stable over calendar time but the number of patients in 2012 and 2015 were low.

Figure 10-2 Cardiovascular and cerebrovascular comorbidity



I = 95% CI

10.4.2 Missing information in the RMP and high risk treatment conditions

The missing information in the Risk Management Plan (RMP) includes use of NVA237 in patients with unstable ischemic heart disease, cardiac arrhythmia and long QT-syndrome, use in patients with liver impairment, use in pregnancy and lactation, long-term use in COPD beyond 1 year, off label use in adults with asthma without COPD and in the pediatric population; and safety and efficacy of alternative dosing regimens. Use in patients with unstable ischemic heart disease, arrhythmia and long QT-syndrome is presented in Section 10.4.1; dosage and treatment duration is described in Section 10.2.3

CKD was assessed either via disease code or based on eGFR. For the pooled data, 45.1% of all new NVA237 initiators had CKD-stage 2 (a creatinine clearance between 60-89 mL/min/1.73m^2) and 20.9% had CKD-stage 3 (eGFR 30-59 mL/min/1.73m^2). Database differences were observed with regard to the prevalence of CKD-stage 3 with the highest proportions for THIN (30.2%) and HSD (32.1%). The proportion of patients with CKD-stage 4 (eGFR 15-29 mL/min/1.73m^2) was low (≤5.0%) and the number of patients with CKD-stage 5 (eGFR< 15 mL/min/1.73m^2 or need of dialysis) was even smaller. See Figure 16-5 for further details.

In the pooled population, the proportion of patients with hepatic impairment was 2.5% (database-specific range: 0.6-5.7%) and the proportion of urinary retention/bladder outflow symptoms was 1.5% (database specific range: 0.8-3.5%). The proportion of patients with narrow-angle glaucoma was very small, namely 0.1% (database specific range: 0.0-0.8%). The proportion of patients with benign prostatic hyperplasia (BPH) was 13.8% in the pooled

population; highest database-specific proportions were observed for Italy (14.7%) and Spain (19.2%).

Breastfeeding and pregnancy were assessed during NVA237 exposure as well as in the year prior to index date (for breastfeeding) and in the 9 months prior to index date (for pregnancy). During NVA237 exposure no pregnant or lactating women were identified. One woman in THIN was identified as lactating in the year prior to start of NVA237.

Database-specific results for missing information in the RMP and high risk treatment conditions are summarized in Table 10-4 below; results by calendar year are available in the appendices (see Table 16-8).

10.4.3 Uninterrupted use of NVA237 for more than one year

Overall, there were 1,261 patients (9.2%) who used NVA237 without interruption for more than one year, namely 285 (13.2%) in THIN, 101 (9.8%) in IPCI, 237 (16.6%) in Aarhus, 141 (4.9%) in HSD and 497 (8.0%) in SIDIAP. Among the subset of patients who had at least one year of follow-up after NVA237 initiation (n=5,952, see last row of Table 10-2), 20.1% used NVA237 without interruption for more than one year.

Table 10-4 Underlying conditions corresponding to population defined in the "Missing information section" of the RMP or who have high risk treatment conditions – by database and pooled

Underlying condition	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Unstable ischemic heart disease (MI and unstable AP)	180 (8.34)	7.24- 9.58	104 (10.15)	8.44-12.15	143 (10.04)	8.59-11.71	144 (5.01)	4.27- 5.87	341 (5.48)	4.94- 6.07	912 (6.65)	6.25- 7.08
LongQT syndrome/Torsade de Pointes	1 (0.05)	0.01- 0.26	1 (0.10)	0.02- 0.55	0 (0.00)	0.00- 0.27	1 (0.03)	0.01- 0.20	0 (0.00)	0.00- 0.06	3 (0.02)	0.01- 0.06
Cardiac arrhythmia*	202 (9.36)	8.20-10.66	120 (11.71)	9.88-13.82	162 (11.38)	9.83-13.13	368 (12.81)	11.64- 14.08	724 (11.63)	10.86- 12.45	1,576 (11.50)	10.97-12.04
UR or sympt bladder outfl. obstruction	75 (3.47)	2.78- 4.33	16 (1.56)	0.96- 2.52	18 (1.26)	0.80- 1.99	22 (0.77)	0.51- 1.16	69 (1.11)	0.88- 1.40	200 (1.46)	1.27- 1.67
Narrow-angle glaucoma	2 (0.09)	0.03- 0.34	0 (0.00)	0.00- 0.37	11 (0.77)	0.43- 1.38	1 (0.03)	0.01- 0.20	1 (0.02)	0.00- 0.09	15 (0.11)	0.07- 0.18
Renal impairment:												
Stage 1 **	2 (0.09)	0.03- 0.34	0 (0.00)	0.00-0.32	0 (0.00)	0.00-0.27	222 (7.73)	6.81- 8.76	0 (0.00)	0.00-0.06	224 (1.63)	1.44- 1.86
Stage 2	1,048 (48.54)	46.44-50.65	475 (46.34)	43.31-49.40	686 (48.17)	45.59- 50.77	1,090 (37.94)	36.18- 39.73	2,886 (46.35)	45.12- 47.59	6,185 (45.12)	44.29-45.96
Stage 3	652 (30.20)	28.30-32.17	119 (11.61)	9.79-13.72	215 (15.10)	13.33- 17.05	923 (32.13)	30.44- 33.86	950 (15.26)	14.39- 16.17	2,859 (20.86)	20.19-21.55
Stage 4	63 (2.92)	2.29- 3.72	8 (0.78)	0.40- 1.53	21 (1.47)	0.97- 2.24	125 (4.35)	3.66- 5.16	70 (1.12)	0.89- 1.42	287 (2.09)	1.87- 2.35
Stage 5	5 (0.23)	0.10- 0.54	0 (0.00)	0-0.32	2 (0.14)	0.04- 0.51	59 (2.05)	1.60- 2.64	7 (0.11)	0.05- 0.23	73 (0.53)	0.42- 0.67
Stage Unknown	23 (1.07)	0.71- 1.59	23 (2.24)	1.50- 3.34	4 (0.28)	0.11- 0.72	8 (0.28)	0.14- 0.55	117 (1.88)	1.57- 2.25	175 (1.28)	1.10- 1.48

Underlying condition	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
No CKD disease***	366 (16.95)	15.43-18.59	400 (39.02)	36.08-42.05	496 (34.83)	32.40- 37.34	446 (15.52)	14.25- 16.89	2,196 (35.27)	34.09- 36.47	3,904 (28.48)	27.73-29.24
Liver disease	95 (4.40)	3.61- 5.35	27 (2.63)	1.82- 3.81	15 (1.05)	0.64- 1.73	164 (5.71)	4.92- 6.62	36 (0.58)	0.42- 0.80	337 (2.46)	2.21- 2.73
Pregnancy within 9 months prior to treatment start	1 (0.05)	0.01- 0.26	0 (0.00)	0.00- 0.37	0 (0.00)	0.00- 0.27	0 (0.00)	0.00- 0.13	0 (0.00)	0.00- 0.06	1 (0.01)	0.00- 0.04
Pregnancy during NVA237	0 (0.00)	0.00- 0.18	0 (0.00)	0.00- 0.37	0 (0.00)	0.00- 0.27	0 (0.00)	0.00- 0.13	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.03
Breastfeeding recorded within 12 months prior to treatment start	0 (0.00)	0.00- 0.18	0 (0.00)	0.00- 0.37	0 (0.00)	0.00- 0.27	0 (0.00)	0.00- 0.13	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.03
Breastfeeding during NVA237	0 (0.00)	0.00- 0.18	0 (0.00)	0.00- 0.37	0 (0.00)	0.00- 0.27	0 (0.00)	0.00- 0.13	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.03

MI=Myocardial infarction; AP=Angina pectoris; UR=Urinary retention;

*AV block, Atrial flutter/fibrillation, ventricular tachycardia/fibrillation, Torsade de Pointes/QTc prolongation;

**Stage 1 based on disease codes for CKD stage 1;

***creatinine clearance above 90 mL/min/1.73m2 or no creatinine values available.

Stage 1=kidney damage w/normal or increased GFR (eGFR ≥90 mL/min/1.73m^2);

Stage 2=kidney damage w/mild reduction of GFR (eGFR 60-89 mL/min/1.73m^2);

Stage 3=moderate reduction of GFR (eGFR 30-59 mL/min/1.73m^2);

Stage 4=severe reduction of GFR (eGFR 15-29 mL/min/1.73m^2);

Stage 5=kidney failure (eGFR <15 mL/min/1.73m^2 or dialysis);

10.4.4 Off-label use of NVA237

Off-label indication of use in patients initiating NVA237

The indication of use in patients initiating NVA237 is presented in Table 10-5 below. For Aarhus, information on the indication of use was only available in approximately half of the patients (44.3%). The information was available based on disease codes retrieved from ambulatory care or hospital admission. In the pooled dataset, the proportion of "potential off-label" use (patients initiating NVA237 for reasons of "asthma only" or for the indication category "other") was 14.5% (95% CI: 13.9-15.2%). By database, the proportion of potential off-label use was 5.0% (95% CI: 3.7-6.8) for Aarhus, 8.4% (95% CI: 7.3-9.7) for THIN, 10.6% (95% CI: 8.8-12.6) for IPCI, 17.1% (95% CI: 16.2-18.2) for SIDIAP and 18.1% (95% CI: 16.7-19.6) for HSD.

For the indication category "other", available disease codes identified around the first-time prescription of NVA237 were reviewed; frequencies and proportions can be found in the appendices (see Figure 16-4). In all databases, the proportion of patients receiving a first-time prescription of NVA237 for reasons of respiratory symptoms (cough, dyspnea, wheezing) (191 out of the total of 744 patients who used NVA237 for "other indications", 25.7%) or lower respiratory tract infections (251/744, 33.7%) was substantial. Still, there were disease codes reported in association with NVA237 prescription that could be considered potentially unrelated to COPD (i.e., disease codes related to symptoms/diseases of the upper respiratory tract or non-respiratory related).

Off-label use due to age

Overall, nine patients (<0.1%) were younger than 18 years at the time of first NVA237 prescription (1 in THIN (0.05%), 1 in IPCI (0.1%), 1 in HSD (0.03%) and 6 (0.1%) in SIDIAP). Further details for these patients are presented in Section 10.5.1 below.

Table 10-5 Indication for NVA237-initiation, as assessed at index date (based on indication found in the patients' medication prescription or medical files) – by database and pooled

Indication of use	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
COPD#	1,415 (67.96)	65.93-69.93	823 (80.61)	78.07-82.92	703 (88.65)	86.25-90.67	2,201 (79.60)	78.06-81.06	3,925 (72.36)	71.16-73.54	9,068 (75.04)	74.26-75.8
Asthma#	103 (4.95)	4.1-5.96	62 (6.07)	4.77-7.71	24 (3.03)	2.04-4.46	271 (9.8)	8.75-10.97	547 (10.08)	9.31-10.91	1,007 (8.33)	7.85-8.84
Asthma and COPD#	491 (22.74)	21.02-24.56	90 (8.81)	7.23-10.71	50 (6.31)	4.82-8.22	63 (2.28)	1.78-2.9	572 (10.55)	9.76-11.39	1,266 (10.48)	9.94-11.03
Other#	73 (3.51)	2.8-4.39	46 (4.51)	3.39-5.96	16 (2.02)	1.25-3.25	229 (8.28)	7.31-9.37	380 (7.01)	6.36-7.72	744 (6.16)	5.74-6.6
Indication of use unknown	77 (3.57)	2.86-4.43	4 (0.39)	0.15-1.00	631 (44.31)	41.75-46.90	108 (3.76)	3.12-4.52	802 (12.88)	12.07-13.74	1,622 (11.83)	11.30-12.38
Potential off-label use*#	176 (8.45)	7.33-9.73	108 (10.58)	8.84-12.61	40 (5.04)	3.73-6.8	501 (18.11)	16.72-19.59	930 (17.15)	16.17-18.17	1,755 (14.52)	13.9-15.16

*Potential off label use is defined as the combination of the "Asthma" and "Other" categories, as per protocol. #Number of patients for whom indication of use is available as denominator

10.5 Other analyses

10.5.1 Pediatric patients

In total, nine study patients were younger than 18 years of age (min-max: 10-17 years) at time of NVA237 initiation. Dosing information was only available for three of these patients; all used NVA237 once daily. Based on information from disease codes, indication of NVA237 use for these nine patients was "unknown" for three, "asthma" for two, "combination of asthma and COPD" for two, and "COPD" for two patients. Diagnostic codes for COPD were reviewed and found to be ICD10 code J40 – "Bronchitis, not specified as acute or chronic". The median duration of NVA237 use for these nine patients was 30 days (min-max: 20-60 days). None of these patients had a medical history of cardiovascular or cerebrovascular comorbidity, and none had any other condition defined as missing information in the RMP.

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).

11 Discussion

11.1 Key results

During the study period (01 November 2012 to 01 March 2015) 13,707 patients having a first-time prescription or dispensation of NVA237 were identified in five European primary care and prescription databases.

NVA237 was prescribed according to the defined dose as per product label (i.e., once daily) in more than 98.0% of first-time NVA237 users in the subset of study patients for which data on dosage was available. It is unclear whether the remaining proportion of patients (<2.0%) reflects true non-compliance in terms of prescribing behavior or whether the relevant treatment episodes resulted due to human error when coding dosage data in patient prescription records.

In the pooled dataset, the indication of use was "COPD" or "COPD and asthma" for 85.5% of patients. This proportion was lower in HSD and SIDIAP where use for asthma or other indications was approximately 20%. If indication of use was missing in the prescription files, disease codes (other than asthma and COPD) were reviewed at the time of prescription of NVA237. Approximately 60% of the "other indications" were related to either respiratory symptoms or lower respiratory tract infection. It is known that lower respiratory tract infections might induce COPD exacerbation, hence prescription of NVA237 due to worsening of COPD symptoms is a possible explanation. Use of NVA237 for asthma only (8.3%) was elevated, however, it is widely accepted that, in primary care, it is difficult to differentiate between asthma and COPD, especially in younger patients (Price and Brusselle 2013).

Consistent with published data about the comorbidity in patients with COPD comorbidity in NVA237 users was common (Smith and Wrobel 2014, van der Molen 2010). In the pooled

dataset, the proportion of cardiovascular comorbidity was as follows: history of cardiac arrhythmia (11.5%), heart failure (9.1%), unstable ischemic heart disease (6.6%), angina pectoris (7.4%), myocardial infarction (5.8%). Although the proportion of patients with cardiac arrhythmia was high, the number of patients with malignant ventricular arrhythmia (=ventricular tachycardia, ventricular fibrillation, and TDP) was low, namely less than 0.5%. Results were comparable within databases apart from a higher prevalence of heart failure in IPCI (14.2%) compared to the other databases (range 7.1-9.2%) and the prevalence of angina pectoris and myocardial infarction which was lower in Italy and Spain (around 3%) and higher in the other databases (range 13.1-16.7%)

A history of stroke was reported in 6.8% of NVA237 users in the pooled dataset and ranged from 4.8 to 10.8% across databases. The proportion of TIA was 3.1% in the pooled dataset and ranged from 2.0 to 5.2% across databases. The proportion of patients with severe or end-stage renal disease was low (add percentage) but the proportion of patients with mild (45.1%) or moderate (20.9%) renal impairment was higher. The prevalence of hepatic impairment, narrow angle glaucoma and urinary retention and/or bladder outflow obstruction was around or below 2.5%. In contrast to the low prevalence of urinary retention/bladder outflow obstruction the prevalence of BPH was much higher (pooled 13.8%) with especially high proportions in HSD and SIDIAP.

No patient was identified as having been pregnant or lactating during NVA237 use. In THIN there was one lactating patient in the year prior to start of NVA237.

No major differences in COPD characteristics (duration of COPD and previous hospitalization for COPD exacerbation) were observed across databases. In the pooled dataset, more than 80% of patients had moderate or severe COPD when assessed by spirometry. For patients without usable spirometry data, COPD severity was assessed by proxy (i.e., according to published algorithms, see Annex 2.4), and these patients were mainly classified as having mild or moderate COPD.

There were obvious country-specific differences in the prescribing behavior of other respiratory medications. Use of other short-acting agents such as SAMA or the combination of SAMA+SABA was much lower than use of 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 and Spain). The fixed combination of LABA+ICS was frequently prescribed (pooled proportion 46.2%) with the highest proportion in the UK (59.1%) and the lowest proportion in Denmark (39.0%).

In the pooled dataset, 31.8% of patients received a systemic corticosteroid in the 6 months prior to index date, with highest proportions for THIN (43.3%) and IPCI (42.2%) and lowest for SIDIAP (26.9%). When considering use of systemic corticosteroids indicated for “COPD exacerbation” only, the pooled proportion was 10.4%, with lowest use in SIDIAP.

11.2 Limitations

The limitations of this study are mainly due to the availability and level of detail of data. Not all potential covariates (i.e. smoking, spirometry data, serum creatinine, indication of use and dosing information) are recorded in all databases and not all available variables can express the optimal level of information desired. Particularly, information on the prescribed dose and

duration of a prescription is not captured directly in all databases, hence necessitating estimation, which could have led to misclassification of exposure.

COPD severity was assessed by spirometry if available and by proxy if information on spirometry was lacking. When assessed by spirometry, the number of patients diagnosed as not having COPD based on spirometry data was high (34.0% in pooled dataset). This does not necessarily mean that patients did not have COPD at the time of NVA237 initiation, as spirometry data up to five years prior to the index date were considered. For Aarhus, only data for FEV1 were available for 28% of study patients; hence, assessment of COPD severity for the Aarhus study population was not possible.

Information on smoking status was retrieved from the databases but in contrast to prospective cohort studies, this information is not necessarily collected in a standardized manner. Indeed the proportion of patients with missing information was high in Aarhus (up to 55%) and HSD (up to 22%). Amongst patients for whom information on smoking status was available, the proportion of non-smokers was high in HSD and SIDIAP compared to the other databases. 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 non-smokers among COPD patients is likely to increase over the coming years, it is difficult to assume that this would only hold for Italy and Spain. In addition, the high proportion of COPD in non-smokers is mainly reported in non-European countries (Salvi and Barnes 2009). With respect to the databases used for this study, data on smoking status is not prospectively collected. The potential for misclassification of smoking, especially between “non-smoking” and “past-smoking”, cannot be ruled out.

All databases used for this study, with the exception of the Aarhus University Prescription Database and SIDIAP, have information on prescription only but not on dispensing or actual medication intake. Exposure data for SIDIAP is based on prescription and dispensing data. For chronic therapy, the patient attends a GP visit for the first prescription, but follow-up medication is dispensed by the pharmacy without need of prescriptions. The exact date of pharmacy dispensing in unknown in SIDIAP, dates are available as month/year with the potential for non-differential misclassification. For all databases, it is actually unknown whether or not the patient took the prescribed product – however, as medication adherence is highest at initiation of therapy, the risk of misclassification of NVA237 exposure is of lesser concern in a new-user design (Lareau and Yawn 2010).

Co-morbidities 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 these databases are suitable for pharmaco-epidemiologic research (Cazzola et al 2011, Ehrenstein et al 2010, Garcia-Gil Mdel et al 2011, Lewis et al 2007, Vlug et al 1999). Still, some 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 compared to the other databases. It is unknown whether or not this is due to real differences in risk of ischemic heart diseases 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 Spain and Italy but this could have been

related to differences in gender distribution between the different NVA237 cohorts. In addition, Aarhus retrieves information on disease codes from hospital data (ambulatory care or hospitalized patients). This implies that the assessed comorbidities, which did not necessarily require secondary or tertiary care (i.e., hepatic impairment, BPH), could have been underreported in Aarhus. 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.

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 complete. As the indication of use was one criterion for "off-label" use, the indication of use of NVA237 was assessed by searching the databases for relevant disease codes (COPD or asthma). For the indication of COPD, we considered the complete medical history of the patient. In the case of asthma, this was only considered as indication of NVA237 use if the recorded date of asthma fell within a maximum of 1 year prior to index date. If NVA237 was prescribed for reasons other than COPD or asthma, the respective disease codes in the month before and after the prescription date were provided. 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 NVA237 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 NVA237, it is difficult to retrieve this information from automated databases especially if based on disease codes only.

Although the number of patients within this report exceeds 3,000 as was originally set as the minimum sample size for the study, the median duration of NVA237 use was still relatively short. Of the patients with at least one year of follow-up since NVA237 start (n=5,952), only ~20% of patients used NVA237 for a continuous period of more than one year. This does not necessarily imply that NVA237 is frequently discontinued but could be related to the method of calculation of episodes of use. Episodes of use were created based on NVA237 prescriptions. In case of a gap of 30+ days between 2 consecutive prescriptions, the treatment episode was discontinued at the stop date of the prescription prior to the gap. Furthermore, in chronic diseases such as COPD, it is known that treatment adherence is low and a result of both intentional and non-intentional non-adherence (Bryant et al 2013).

For this final study report, results are provided by database, pooled, and by calendar year. Interpretation by calendar year proved to be less meaningful as the number of patients in 2012 (0.5%) and 2015 (0.7%) were low compared to the total number of patients. In addition, results for 2012 reflect data from Aarhus only, while results for 2015 reflect data from THIN and IPCI only.

11.3 Interpretation

For this final report, 13,707 new users of NVA237 were identified. From the available data, we made the following observations. The study population at time of first prescription was somewhat older than the population included in randomized controlled trials (RCTs) on

LAMA use (mean age pooled 69.9 years in this study vs. 63.4-65.0 in RCTs) (Agusti et al 2010, D'Urzo et al 2011, Kerwin et al 2012, Wise et al 2013). With respect to gender distribution, a male preponderance was found in Italy (HSD) and Spain (SIDIAP), whereas distribution of females and males in the three remaining countries was relatively balanced. Older epidemiological studies have shown that the incidence and prevalence of COPD is higher in men compared to women (Siafakas et al 1995, Aryal et al 2013). However, more recent studies have shown that rates of smoking and COPD diagnosis in women are increasing. In Italy and Spain, the majority of first-time NVA237 users is male and in these countries the majority of smokers is also male (Rycroft et al 2012, Aryal et al 2013).

The proportion of COPD exacerbations either requiring hospitalization or treatment with systemic corticosteroids was relatively low; these cohort characteristics were also found to be lower than those reported in RCTs with glycopyrronium bromide and the observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort study (range 20-25%) (D'Urzo et al 2011, Kerwin et al 2012, Agusti et al 2010). However, it must be noted that both the RCTs and the ECLIPSE study mainly recruited patients from secondary care, thereby including study patients with more severe COPD. In addition, information on hospitalization for COPD exacerbation might be incomplete for those databases where no automatic linkage with hospital admission data is possible (THIN (UK), IPCI (NL) and HSD (IT)). The proportion of patients with mild COPD, assessed via spirometry, was low (pooled 8.9%), which indicates that NVA237 is being prescribed to patients with moderate-to severe COPD, as per product label. In addition, spirometry data up to 5 years prior to the index date was used. As COPD is a progressive disease, the proportion of patients with mild COPD might even be lower for those patients who did not have spirometry data close to the index date.

Although the number of patients with underlying cardiovascular and cerebrovascular co-morbidity was seemingly high, it is known from other studies that the prevalence of underlying cardio- and cerebrovascular co-morbidity is high in patients with COPD. Indeed, a recent literature review by Smith et al. on comorbidities in patients with COPD reported prevalences of cardiovascular and cerebrovascular comorbidity (heart failure 5-24%, ischemic heart disease (AP and MI combined) 16-53%, stroke 7%) which are in line with our data (Smith and Wrobel 2014). A recent meta-analysis on the safety of glycopyrronium bromide compared to tiotropium or placebo reported that only ~10% of patients included in the pooled NVA237 clinical trial population had no cerebro-cardiovascular risk factors at baseline (D'Urzo et al 2015). 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 co-morbidities including cerebro- and cardiovascular disease (GOLD 2016).

For those patients where we had information on serum creatinine or CKD disease stage, the proportion of patients with creatinine clearance <90 mL/min/1.73 m^2 was high. Indeed, almost 50.0% of patients had a clearance between 60-89 mL/min/1.73m^2 and approximately one third of study patients, especially in the UK and Italy, had a serum creatinine clearance between 30-59 mL/min/1.73m^2. The proportions observed are not surprising in view of the distributions of age and underlying co-morbidities (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/1.73m^2) for at least 3 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). Our findings are in line with a recent study investigating the prevalence of CKD in Japanese patients with COPD, which reported that 31% of patients had an eGFR<60 mL/min/1.73m^2 (Yoshizawa et al 2015). Furthermore, a European study that investigated the relationship between COPD and CKD in a large cohort of vascular surgery patients with peripheral arterial disease reported that 27% of study patients had a eGFR<60 mL/min/1.73m^2 (van Gestel et al 2009). According to the SmPC, NVA237 can be used at the recommended dose in patients with mild-to-moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, NVA237 should be used only if the expected benefit outweighs the potential risk.

The proportion of patients with other underlying co-morbidities of interest, i.e., hepatic impairment, narrow-angle glaucoma, and urinary retention or bladder outflow symptoms, which are currently indicated as "missing" information as per RMP, were relatively small. The proportion of patients with BPH was higher, but not all of these patients had obstruction recorded as a symptom, which is confirmed by the low prevalence of patients with urinary retention or bladder outflow symptoms. There were no pregnant or lactating women identified during use of NVA237 and there was one patient who reported breastfeeding but prior to NVA237 start. NVA237 is registered for the treatment of COPD, but indication of use of NVA237 other than COPD or "COPD and asthma" was relatively higher in Italy (HSD) and Spain (SIDIAP) compared to the other countries. For those patients where the indication of use was different from COPD or asthma, the disease codes at time of NVA237 prescription were reviewed; in approximately 60% of these patients, NVA237 was prescribed for respiratory symptoms or lower respiratory tract infections. It is reasonable to assume that these respiratory symptoms (e.g., coughing, dyspnea) are related to underlying COPD, but that COPD diagnoses were not coded (Cillessen and de Vries Robbe 2012). In addition, we know that LRTIs increase the risk of COPD exacerbation, thus it is also possible that prescription of NVA237 for LRTI could be a proxy of underlying COPD (Wark et al 2013). This would imply that the proportion of "off-label" use reported in this study is likely to be overestimated.

Other criteria for "off-label use" were use of alternative dosing regimens or use in patients younger than 18 years. For those databases where information on dosing was available, the majority (>98.0%) of patients used NVA237 once daily. Alternative dosing regimens were infrequent, but it is unclear whether this is an entry error or a true deviation from the recommended dosing. Within the study cohort, nine patients (<0.1% of the pooled study population) were younger than 18 years of age at the time of first-prescription of NVA237.

Although the number of patients within this report exceeds 3,000, which was originally set as the minimum study sample size, the median duration of NVA237 use was still relatively low (i.e., only ~10% of patients used NVA237 for a consecutive period of more than one year. The majority of main objectives in this DUS relate to the description of patient characteristics at time of NVA237-initiation (and not during follow-up), we are convinced that the study sample size used for this final analysis was large enough to answer these questions. In

addition, although only 1,261 patients used NVA237 for more than 1 year, 5,952 of all NVA237 patients had at least one year of data-follow-up since NVA237 initiation; hence, the criterion for study discontinuation was fulfilled.

Finally, some country-specific differences in relation to the prescription of short- and long-acting bronchodilating products were observed, e.g., very high use of SABA in UK (THIN), very low use of SAMA in Italy (HSD), very low or no use of fixed combination of SABA+SAMA in the UK (THIN) and Spain (SIDIAP). These differences can be explained by local policies (e.g., the recommendation of the Joint Formulary Committee of the British National Formulary, which stating that "the fixed combination of ipratropium+salbutamol is less suitable for prescribing") but also by differences in marketing strategies and market uptake (Committee 2013). The prescribing of LABA and LAMA was comparable between countries except in the UK (THIN) where prescription of single-use LABA was much lower than single-use LAMA. In the UK (THIN), mainly the fixed combination of LABA+ICS was prescribed. This has also been described by other research groups (Wurst et al 2014). Also, use of LABA+ICS was found in 40-50% of patients treated at or during the six months prior to index date); this proportion was approximately two-to-three times lower in Italy (HSD) compared to the other countries.

12 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 NVA237 in various European regions, generalizability may not be appropriate for results for which differences between the databases have been observed.

13 Other information

A teleconference with the Scientific Advisory Committee (SAC) was held on 02 March 2016 to discuss the final study report.

With regard to underlying comorbidity, the SAC suggested to not only look at individual comorbidity, but to also create one variable combining overall cardiovascular comorbidity (combination of ischemic heart disease, heart failure and cardiac arrhythmia) and one variable on comorbidity with limited information in the RMP (combination of urinary retention/bladder outflow obstruction, narrow angle glaucoma, hepatic impairment and kidney impairment). In addition, the SAC suggested quantifying and describing the number of patients who use other LAMAs in combination with NVA237 at time of index date. Use of other respiratory drugs, including LAMA, is currently described in the six-months prior to and including the index date, but not separately for use on the index date only. Attention was drawn to the fact that both suggested analyses were not foreseen in the study prototcol or Statistical Analysis Plan (SAP). The SAC appreciated that the study data were analysed in line with the PRAC-approved protocol and Statistical Analysis Plan.

Other comments and suggestions raised by the SAC with regard to the interpretation and limitations of the results have been incorporated in the report.

14 Conclusion

During the study period we identified 13,707 incident users of NVA237, of which 1,261 (9.2%) had used NVA237 for a consecutive period of more than one year.

Prescription of NVA237 to patients with high risk treatment conditions (i.e., patients with severe renal impairment, liver impairment, narrow angle glaucoma, urinary retention, unstable ischemic heart disease and severe cardiac ventricular arrhythmia) was low. Higher proportions of study patients were found to have underlying cerebro- cardiovascular comorbidity and mild to moderate CKD, yet these proportions seem to be in line with reported prevalence estimates for the COPD population, as found in the published literature.

Off-label use with regard to indication of use was present, however, mainly reflects inconsistency of disease coding (NVA237 prescribed for respiratory symptoms or worsening of symptoms because of LRTI). The proportion of patients prescribed NVA237 who were below 18 years of age was extremely small. The results of this final report show that the majority of first-time prescriptions for NVA237 were in line with the product label.

15 References (available upon request)

Afonso AS, Verhamme KM, Stricker BH, et al (2011) Inhaled anticholinergic drugs and risk of acute urinary retention. BJU Int; 107:1265-72.

Agusti A, Calverley PM, Celli B, et al (2010) Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res; 11:122.

Aryal S, Diaz-Guzman E, Mannino DM (2013) COPD and gender differences: an update. Transl Res; 162:208-18.

Bateman ED, Hurd SS, Barnes PJ, et al (2008) Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J; 31(1):143-78.

Bryant J, Mcdonald VM, Boyes A, et al (2013) Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. Respir Res; 14:109.

Camm AJ, Kirchhof P, Lip GY, et al (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J; 31(19):2369-429.

Casson RJ, Chidlow G, Wood JP, et al (2012) Definition of glaucoma: clinical and experimental concepts. Clin Experiment Ophthalmol; 40:341-9.

Cazzola M, Puxeddu E, Bettoncelli G, et al (2011) The prevalence of asthma and COPD in Italy: a practice-based study. Resp Med; 105(3):386-91.

Cazzola M, Calzetta L, Bettoncelli G, et al (2012) Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. Respir Med; 106:249-56.

Committee of the British National Formulary (BNF) 66 (2013) BMJ Publishing Group Ltd and Royal Pharmaceutical Society.

Cricelli C, Mazzaglia G, Samani F, el al (2003) Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. J Public Health Med; 25(3):254-7.

De Lorgeril M, Salen P, Paillard F, et al (2002) Mediterranean diet and the French paradox: two distinct biogeographic concepts for one consolidated scientific theory on the role of nutrition in coronary heart disease. Cardiovasc Res; 54:503-15.

Dickstein K, Cohen-Solal A, Filippatos G, et al (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Eur Heart J; 29(19):2388-442.

Divo M, Cote C, De Torres JP, et al (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med; 186:155-61.

Dong YH, Lin HH, Shau WY, et al (2013) Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease; systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax; 68(1):48-56.

D'urzo A, Ferguson GT, Van Noord JA, et al (2011) Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respir Res; 12:156.

D'urzo AD, Kerwin EM, Chapman KR, et al (2015) Safety of inhaled glycopyrronium in patients with COPD: a comprehensive analysis of clinical studies and post-marketing data. Int J Chron Obstruct Pulmon Dis ; 10:1599-612.

Easton JD, Saver JL, et al (2009) Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke; 40(6):2276-93.

European Commission (EC) (2012) Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge. Project reference No. 215847 (Internet) Available from: <http://cordis.europa.eu/project/rcn/85424_en.html> (Accessed: 18-Mar-2016)

Ehrenstein V, Antonsen S, and Pedersen L (2010). Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol; 2:273-9.

EMA (2013) The ENCePP Code of Conduct – revision 3/EMA/929209/2011.

EMA/CHMP (2005) Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function. 17 Feb2005, CPMP/EWP/2339/02, 10 pages.

ESH/ESC (2007) Summary of the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for the management of arterial hypertension. Vasc Health Risk Manag. 2007;3(6):783-95.

ENCePP (2014) The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Code of Conduct (21-Feb-2014) EMA/929209/2011(Internet) Available from: <http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3.pdf> (Accessed: 20-Mar-2016).

ENCePP (2015) The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 4, 2015). EMA/95098/2010 (Internet) Available from: <http://www.encepp.eu/standards_and_guidances> (Accessed: 20-Mar-2016).

Feary JR, Rodrigues LC, Smith CJ, et al (2010) Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. Thorax; 65:956-62.

Filippi A, Vanuzzo D, Bignamini AA, et al. (2005) The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. Ital Heart J; 6(4):311-4.

Fox K, Garcia MA, Ardissino D, et al (2006) Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J; 27(11):1341-81.

Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al (2011) Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care; 19(3):135-45.

Garcia-Olmos, L., Alberquilla, A., Ayala, V., et al. (2013). Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. BMC Fam Pract, 14, 11.

GOLD (2011) Global strategy for diagnosis, management, and prevention of COPD – updated 2011

GOLD (2016) Global strategy for diagnosis, management, and prevention of COPD – updated 2016 (Internet) Available from: <http://www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016(1).pdf> (Accessed: 18-Mar-2016).

Goldstein LB, Bushnell CD, Adams RJ, et al (2011) Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; 42(2):517-84.

Halbert RJ, Natoli JL, Gano A, et al (2006) Global burden of COPD: systematic review and meta-analysis. Eur Respir J; 28:523-32.

ISPE (2008) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 17:200-8.

Jara M, Lanes SF, Wentworth C, et al (2007) Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. Drug Saf; 30:1151-60.

Jara M, Wentworth C, Lanes S (2012) A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD. BMJ Open; 2(3):e000841.

Juliao AA, Plata M, Kazzazi A, et al (2012) American Urological Association and European Association of Urology guidelines in the management of benign prostatic hypertrophy: revisited. Curr Opin Urol; 22:34-9.

Kerwin E, Hebert J, Gallagher N, et al (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J; 40:1106-14.

Lareau SC, Yawn BP (2010) Improving adherence with inhaler therapy in COPD. Int J Chron Obstruct Pulmon Dis; 5:401-6.

Lee TA, Pickard AS, Au DH, et al (2008) Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med; 149(6):380-90.

Levey AS, Stevens LA, Schmid CH, et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med; 150:604-12.

Levey AS, Coresh J (2012) Chronic kidney disease. Lancet; 379:165-80.

Lewis JD, Schinnar R, Bilker WB, et al (2007) Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf; 16(4):393-401.

Maclay JD, Macnee W (2013) Cardiovascular disease in COPD: mechanisms. Chest; 143:798-807.

Michele TM, Pinheiro S, Iyasu S (2010) The safety of tiotropium--the FDA's conclusions. N Engl J Med; 363(12):1097-9.

Miller J, Edwards LD, Agusti A, et al (2013) Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med; 107:1376-84.

Pauwels RA, Buist AS, Calverley PM, et al (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med; 163(5):1256-76.

Price D and Brusselle G (2013) Challenges of COPD diagnosis. Expert Opin Med Diagn; 7(6):543-56; Epub 2013 Oct 8.

Rycroft CE, Heyes A, Lanza L, et al (2012) Epidemiology of chronic obstructive pulmonary disease: a literature review. Int J Chron Obstruct Pulmon Dis; 7:457-94.

Salvi SS, Barnes PJ (2009) Chronic obstructive pulmonary disease in non-smokers. Lancet; 374:733-43.

Schneider C, Bothner U, Jick SS, et al (2010) Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur J Epidemiol; 25:253-60.

Siafakas NM, Vermeire P, Pride NB, et al (1995) Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J; 8:1398-420.

Singh D (2015) New combination bronchodilators for chronic obstructive pulmonary disease: current evidence and future perspectives. Br J Clin Pharmacol; 79:695-708.

Singh S, Loke YK, Enright PL, et al (2011) Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ; 342:d3215.

Singh S, Loke YK, Furberg CD (2008) Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA; 300(12):1439-50.

Smith MC, Wrobel JP (2014) Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis; 9:871-888.

Sorensen HT, Larsen BO (1994) A population-based Danish data resource with possible high validity in pharmacoepidemiological research. J Med Syst; 18(1):33-8.

Suruki R, Sampson T,Muellerova H (2009) Examination of corrected QT intervals among participants with COPD in NHANES III. Am J Respir Crit Care Med 179; 2009:A4529

Thygesen K, Alpert JS, Jaffe AS, et al (2012) Third universal definition of myocardial infarction. Eur Heart J; 33(20):2551-67.

Van Blijderveen JC, Straus SM, Zietse R, et al (2013) A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands. Int Urol Nephrol. 2014 Mar;46(3):583-92. doi: 10.1007/s11255-013-0563-3. Epub 2013 Sep 27.

Van Der Molen T (2010) Co-morbidities of COPD in primary care: frequency, relation to COPD, and treatment consequences. Prim Care Respir J; 19:326-34.

Van Gestel YR, Chonchol M, Hoeks SE et al (2009) Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients. Nephrol Dial Transplant 2009; 24(9):2763-7; Epub 2009 Apr 15.

Verhamme KM, Afonso A, Romio S, et al (2013) Use of tiotropium Respimat Soft Mist Inhaler versus Handihaler and mortality in patients with COPD. Eur Respir J; 42(3): 606-15.

Verhamme KM, Afonso AS, van Noord C, et al (2012) Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. Pulm Pharmacol Ther; 25(1):19-26.

Verhamme KM, Sturkenboom MC, Stricker BH, et al (2008) Drug-induced urinary retention: incidence, management and prevention. Drug Saf; 31:373-88.

Vlug AE, van der Lei J, Mosseveld BM, et al (1999) Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med; 38(4-5):339-44.

Wark PA, Tooze M, Powell H, et al (2013) Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission. Respirology; 18:996-1002.

WHO Expert Committee (2008) The selection and use of essential medicines. World Health Organ Tech Rep Ser; (950):backcover, vii-174.

Wise RA, Anzueto A, Cotton D, et al (2013) Tiotropium Respimat Inhaler and the risk of death in COPD. N Engl J Med; 369(16):1491-501.

Wurst KE, Punekar YS, Shukla A (2014) Treatment evolution after COPD diagnosis in the UK primary care setting. PLoS One; 9:e105296.

Yoshizawa T, Okada K, Furuichi S, et al (2015) Prevalence of chronic kidney diseases in patients with chronic obstructive pulmonary disease: assessment based on glomerular filtration rate estimated from creatinine and cystatin C levels. Int J Chron Obstruct Pulmon Dis; 10:1283-9.

Zipes DP, Camm AJ, Borggrefe M, et al (2006) ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol; 48(5):e247-346.

16 Appendices

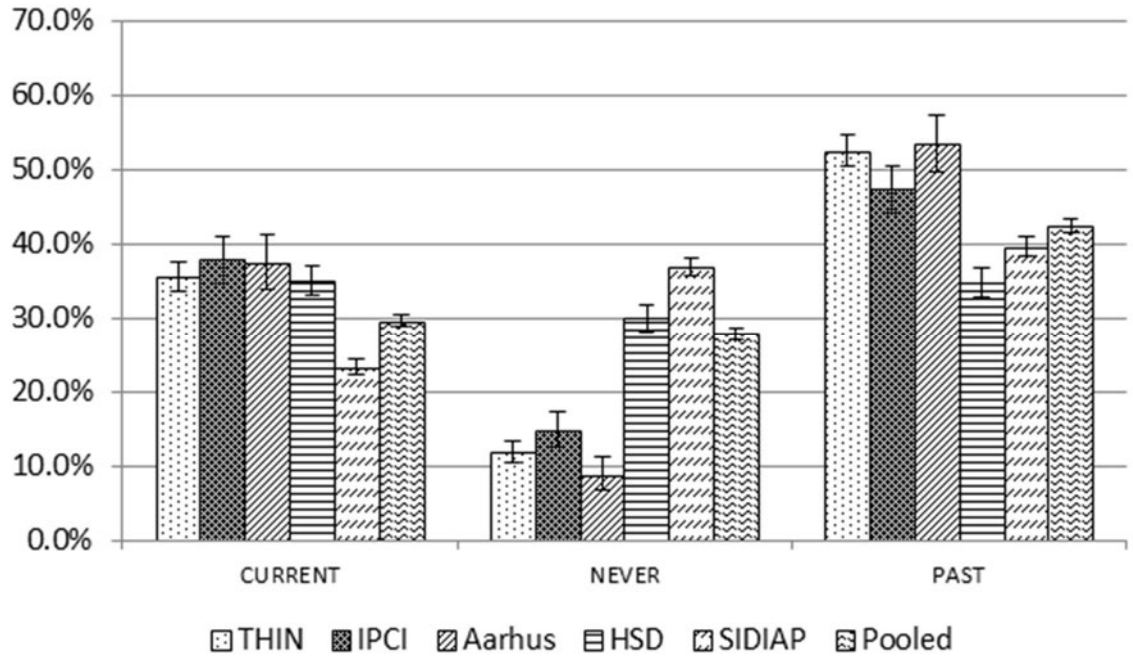
Annex 1 – List of stand-alone documents

There are no stand-alone documents.

Annex 2 – Additional information

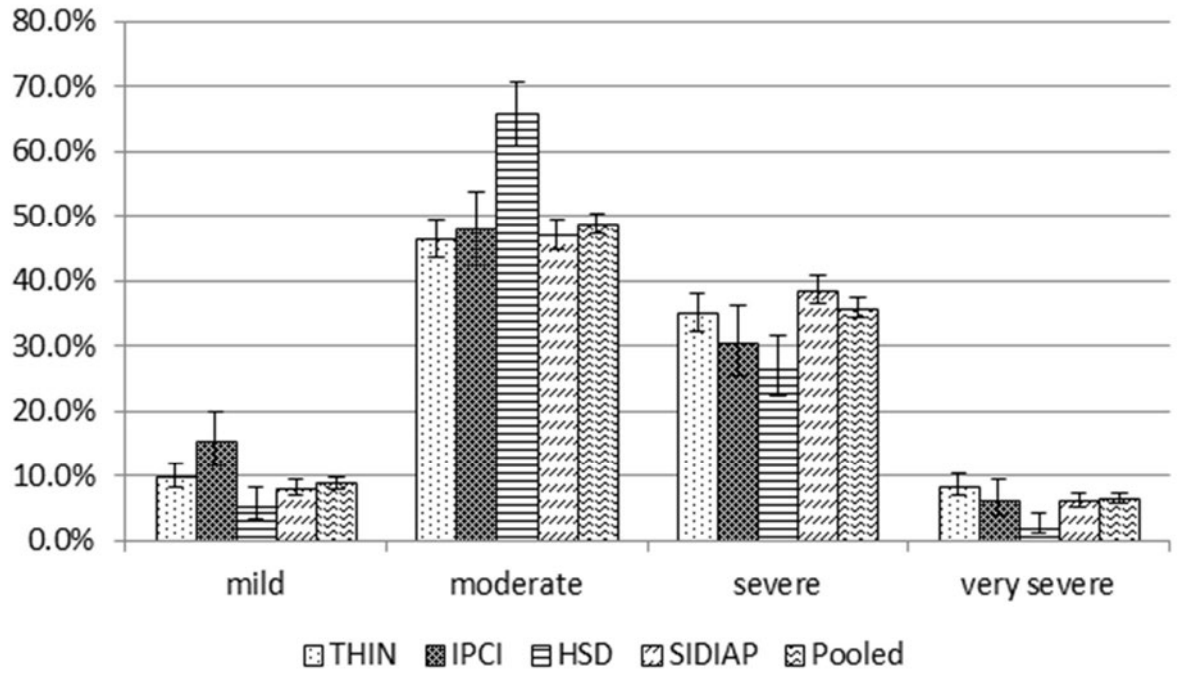
Annex 2.1 – Additional results tables and figures

Figure 16-1 Smoking status



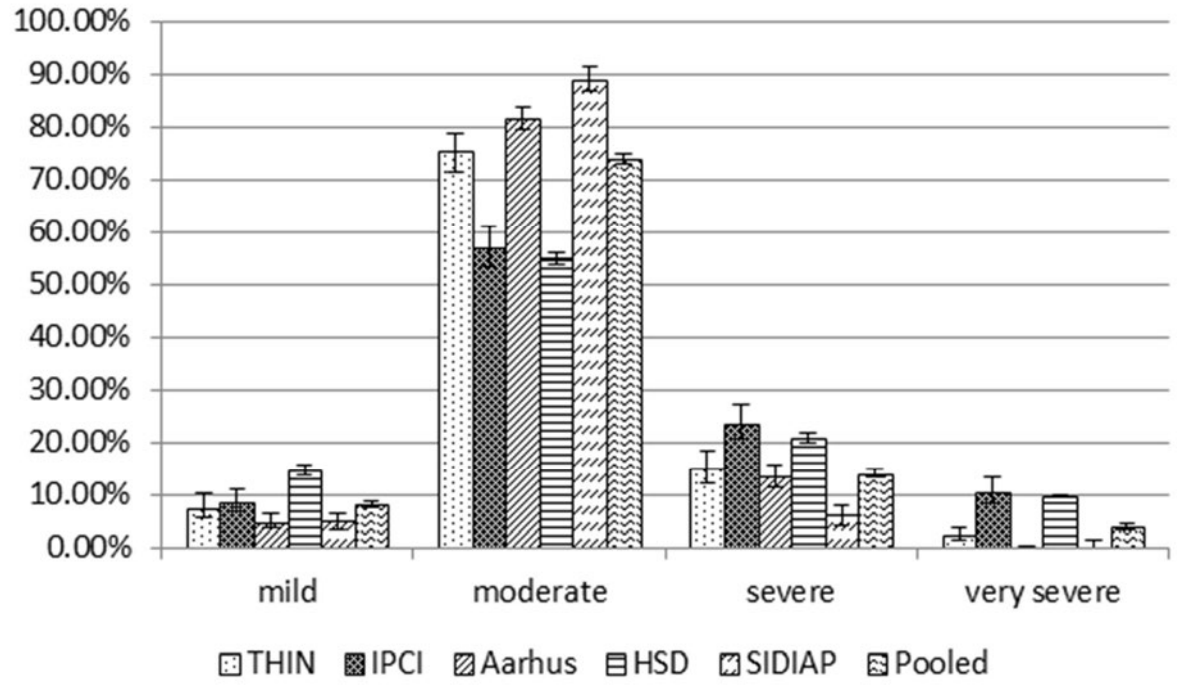
I = 95% CI

Figure 16-2 COPD severity by spirometry



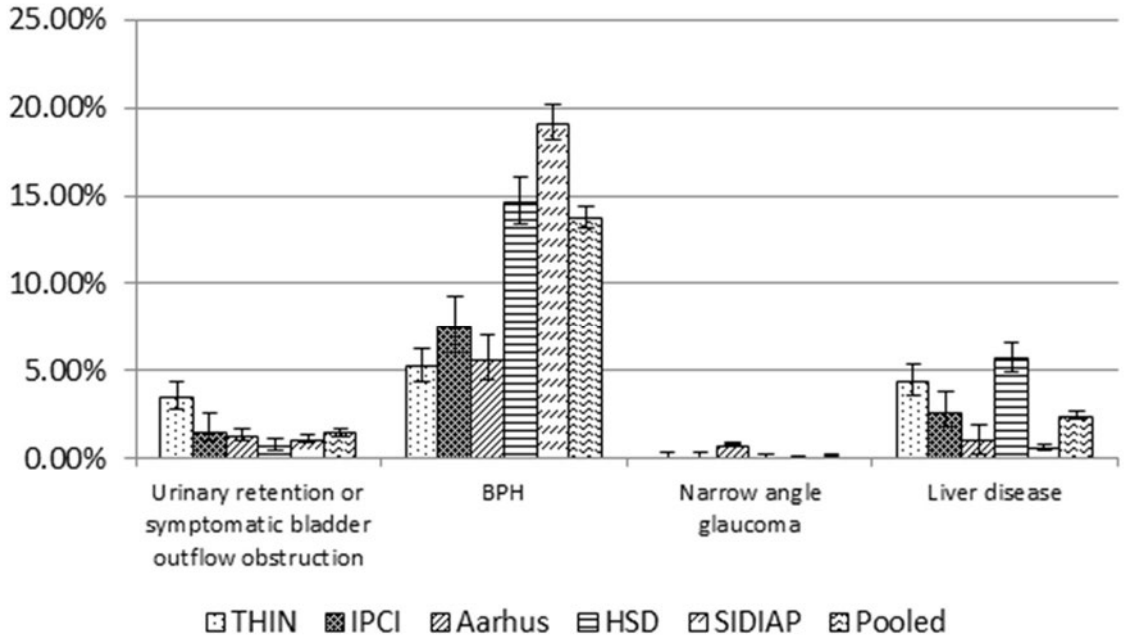
I = 95% CI

Figure 16-3 COPD severity by proxy



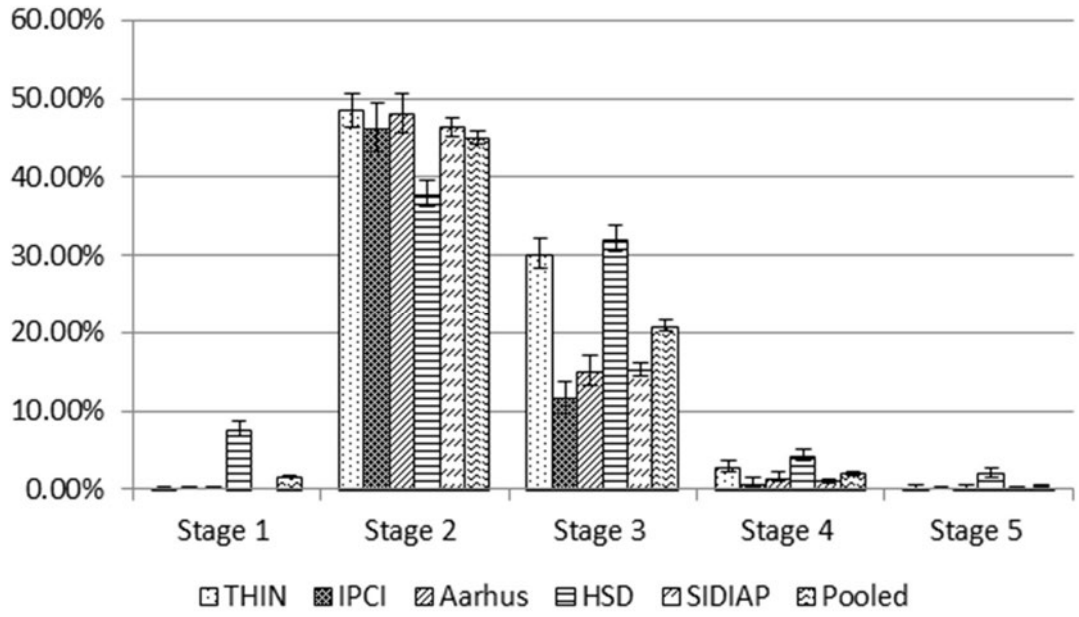
I = 95% CI

Figure 16-4 Proportions of NVA237-initiators with other undelying comorbidities, by database



I= 95% CI

Figure 16-5 Proportions of NVA237-initiators with CKD, by stage and database



I= 95% CI;

CKD stage is based on both disease codes and lab results – For stage 1, based on disease codes for stage 1 only

Stage 1=kidney damage w/normal or increased GFR (eGFR ≥90 mL/min/1.73m^2);

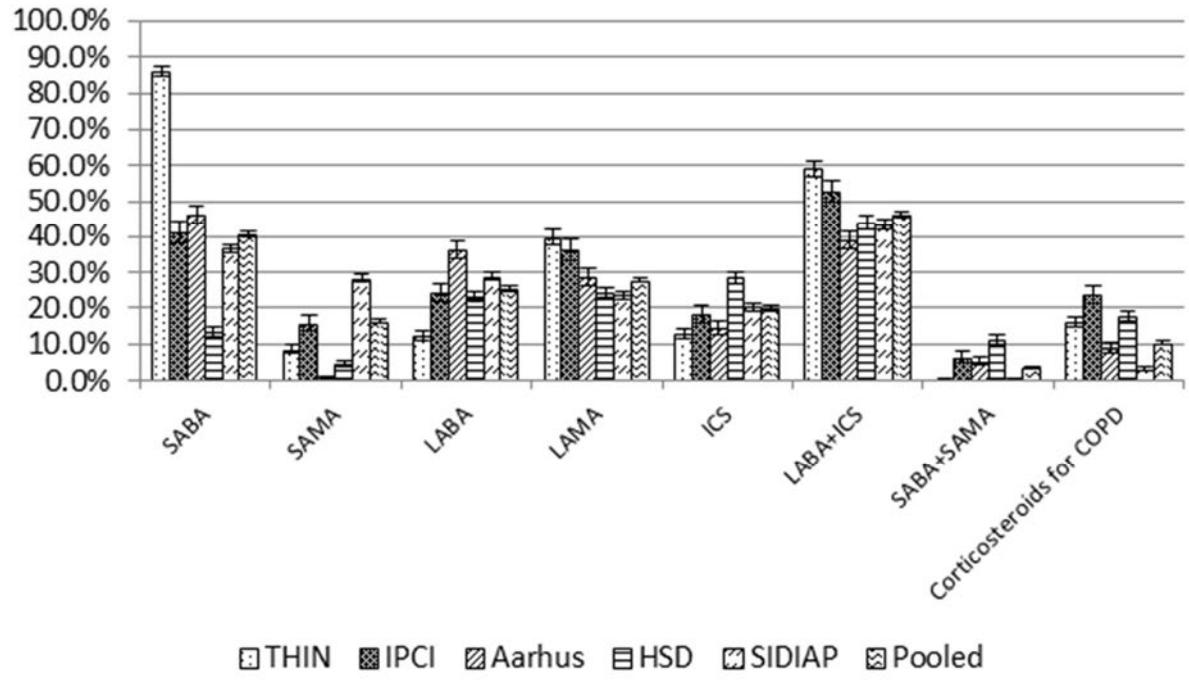
Stage 2=kidney damage w/mild reduction of GFR (eGFR 60-89 mL/min/1.73m^2);

Stage 3=moderate reduction of GFR (eGFR 30-59 mL/min/1.73m^2);

Stage 4=severe reduction of GFR (eGFR 15-29 mL/min/1.73m^2);

Stage 5=kidney failure (eGFR <15 mL/min/1.73m^2 or dialysis);

Figure 16-6 Use of respiratory medications assessed in the six months prior to index date



I = 95% CI

Table 16-1 Baseline characteristics of the NVA237 cohort – by calendar year

Characteristic	2012 (N=72)		2013 (N=6,384)		2014 (N= 7,148)		2015 (N=103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Database								
THIN [UK]	0 (0.00)	0.00-5.07	1,004 (15.73)	14.85-16.64	1,059 (14.74)	13.94-15.58	96 (93.2)	86.63-96.67
IPCI [NL]	0 (0.00)	0.00-5.07	616 (9.65)	8.95-10.4	402 (5.6)	5.09-6.15	7 (6.80)	3.33-13.37
Aarhus [DK]	72 (100)	94.93-100.00	855 (13.39)	12.58-14.25	497 (6.92)	6.35-7.53	0 (0.00)	0.00-3.6
HSD [IT]	0 (0.00)	0.00-5.07	1,065 (16.68)	15.79-17.62	1,808 (25.17)	24.18-26.18	0 (0.00)	0.00-3.6
SIDIAP [ES]	0 (0.00)	0.00-5.07	2,844 (44.55)	43.33-45.77	3,382 (47.08)	45.92-48.23	0 (0.00)	0.00-3.6
Gender								
Female	37 (51.39)	40.07-62.57	2,514 (39.38)	38.19-40.58	2,888 (40.40)	39.27-41.55	58 (56.31)	46.68-65.49
Male	35 (48.61)	37.43-59.93	3,870 (60.62)	59.42-61.81	4,260 (59.60)	58.45-60.73	45 (43.69)	34.51-53.32
Age Categories								
<18	0 (0.00)	0.00-5.07	3 (0.05)	0.02- 0.14	6 (0.08)	0.04- 0.18	0 (0.00)	0.00-3.6
18 < 40	0 (0.00)	0.00-5.07	85 (1.33)	1.08- 1.64	113 (1.58)	1.32- 1.90	1 (0.97)	0.17- 5.30
40 < 60	10 (13.89)	7.72-23.71	1,090 (17.07)	16.17-18.02	1,273 (17.81)	16.94-18.71	19 (18.45)	12.14-27.02
60 - 80	50 (69.44)	58.05-78.87	3,922 (61.43)	60.23-62.62	4,221 (59.05)	57.91-60.19	62 (60.19)	50.54-69.12
> 80	12 (16.67)	9.80-26.91	1,284 (20.11)	19.15-21.11	1,535 (21.47)	20.54-22.44	21 (20.39)	13.74-29.17
Smoking status								
Missing	58 (80.56)	69.97-88.05	944 (14.79)	13.94-15.68	773 (10.81)	10.12-11.56	0 (0.00)	0.00-3.6
Current smoker	6 (42.86)	21.38-67.41	1,567 (28.81)	27.62-30.02	1,928 (30.24)	29.13-31.38	38 (36.89)	28.20-46.53
Past smoker	0 (0.00)	0.00-5.07	1,466 (26.95)	25.79-28.14	1,858 (29.15)	28.04-30.27	5 (4.85)	2.09-10.86
Non-smoker	8 (57.14)	32.59-78.62	2,407 (44.25)	42.93-45.57	2,589 (40.61)	39.41-41.82	60 (58.25)	48.60-67.31

CI=confidence interval

Table 16-2 COPD characteristics (assessed at or during the year prior to index date) – by database and pooled

Characteristic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	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 (%)	1,769 (81.94)	80.26-83.50	367 (35.80)	32.93-38.79	399 (28.02)	25.75-30.41	772 (26.87)	25.28-28.52	3,040 (48.83)	47.59-50.07	6,347 (46.3)	45.47-47.14
Mean (SD)	60.78 (21.22)		62.78 (22.56)		51.86 (17.72)		69.74 (18.28)		60.65 (19.77)		61.36 (20.42)	
Median (IQR)	60 (45.1-72.74)		61.5 (46.44-78.10)		49 (38-64)		70 (58-80.15)		59.44 (46-73)		60.00 (46.00-74.00)	
Min-Max	18.65-225.68		10.00-150.9		25.00-102.00		25.00-125.00		25.00-125.00		0.88-225.68	
No. of patients available for analysis of COPD severity	1,572 (72.81)	70.9-74.65	357 (34.83)	31.97-37.8	n.a.	n.a.	689 (23.98)	22.46-25.58	2,947 (47.33)	46.1-48.58	5,565 (40.6)	39.78-41.42
No COPD (FEV_1/FVC>70)	447 (28.44)	26.26-30.72	76 (21.29)	17.36-25.83	n.a.	n.a.	344 (49.93)	46.20-53.65	1,023 (34.71)	33.02-36.45	1,890 (33.96)	32.73-35.22
Mild	111 (9.87)	8.26-11.75	43 (15.30)	11.56-19.98	n.a.	n.a.	18 (5.22)	3.33-8.10	154 (8.00)	6.87-9.30	326 (8.87)	7.99-9.83
Moderate	524 (46.58)	43.68-49.50	135 (48.04)	42.27-53.87	n.a.	n.a.	228 (66.09)	60.94-70.88	909 (47.25)	45.02-49.48	1,796 (48.87)	47.26-50.49
Severe	395 (35.11)	32.38-37.95	86 (30.60)	25.51-36.22	n.a.	n.a.	92 (26.67)	22.28-31.57	744 (38.67)	36.52-40.87	1,317 (35.84)	34.30-37.40
Very severe	95 (8.44)	6.96-10.21	17 (6.05)	3.81-9.47	n.a.	n.a.	7 (2.03)	0.99-4.13	117 (6.08)	5.10-7.24	236 (6.42)	5.67-7.26

Characteristic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	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	587 (27.19)	25.35-29.1	668 (65.17)	62.2-68.03	1,424 (100)	99.73-100	2,184 (76.02)	74.42-77.54	3,279 (52.67)	51.42-53.9	8,142 (59.4)	58.58-60.22
No COPD	79 (13.46)	10.93-16.46	52 (7.78)	5.99-10.07	280 (24.48)	22.07-27.05	353 (16.16)	14.68-17.77	956 (29.16)	27.62-30.73	1731 (21.26)	20.39-22.16
Mild	38 (7.48)	5.50-10.10	53 (8.60)	6.64-11.08	55 (4.81)	3.71-6.21	269 (14.69)	13.14-16.39	113 (4.86)	4.06-5.82	517 (8.06)	7.42-8.76
Moderate	383 (75.39)	71.47-78.94	352 (57.14)	53.20-60.99	936 (81.82)	79.48-83.95	1,006 (54.94)	52.66-57.21	2,069 (89.07)	87.73-90.27	4,746 (74.03)	72.94-75.09
Severe	76 (14.96)	12.12-18.32	146 (23.70)	20.51-27.22	153 (13.37)	11.52-15.47	381 (20.81)	19.01-22.73	141 (6.07)	5.17-7.12	897 (13.99)	13.16-14.86
Very Severe	11 (2.17)	1.21-3.84	65 (10.55)	8.37-13.23	0 (0)	0-0.33	175 (9.56)	8.29-10.99	0 (0)	0-0.17	251 (3.92)	3.47-4.42
No. of COPD exacerbations requiring hospitalization in the one year prior to the index date												
Mean (SD)	0.06 (0.27)		0.08 (0.33)		0.12 (0.61)		0 (0.09)		0.05 (0.33)		0.05 (0.33)	
Median (IQR)	0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)	
Min-max	0-5		0-3		0-11		0-2		0-10		0-11	
COPD exacerbations requiring hospitalization in the year prior to index date												
None	2,057 (95.28)	94.30-96.09	963 (93.95)	92.32-95.25	1,320 (92.70)	91.23-93.94	2,863 (99.65)	99.36-99.81	5,992 (96.24)	95.74-96.69	13,195 (96.26)	95.93-96.57
1	89 (4.12)	3.36-5.05	49 (4.78)	3.63-6.26	72 (5.06)	4.03-6.32	6 (0.21)	0.10-0.45	165 (2.65)	2.28-3.08	381 (2.78)	2.52-3.07

Characteristic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
2	11 (0.51)	0.28-0.91	10 (0.98)	0.53-1.79	22 (1.54)	1.02-2.33	4 (0.14)	0.05-0.36	47 (0.75)	0.57-1.00	94 (0.69)	0.56-0.84
3 or more	2 (0.09)	0.03-0.34	3 (0.29)	0.10-0.86	10 (0.70)	0.38-1.29	0 (0.00)	0.00-0.13	22 (0.35)	0.23-0.53	37 (0.27)	0.20-0.37
Number of systemic steroid episodes for the treatment of COPD in the year prior to index date												
0	1,709 (79.16)	77.39-80.82	734 (71.61)	68.77-74.29	1,273 (89.40)	87.69-90.89	2,243 (78.07%)	76.52-79.55	5,979 (96.03)	95.52-96.49	11,938 (87.09%)	86.52-87.65
1	327 (15.15)	13.70-16.72	169 (16.49)	14.34-18.88	123 (8.64)	7.29-10.21	423 (14.72%)	13.47-16.07	239 (3.84)	3.39-4.35	1,281 (9.35%)	8.87-9.84
2	84 (3.89)	3.15-4.79	75 (7.32)	5.88-9.08	23 (1.62)	1.08-2.41	110 (3.83%)	3.19-4.59	8 (0.13)	0.07-0.25	300 (2.19%)	1.96-2.45
3 or more	39 (1.81)	1.32-2.46	47 (4.59)	3.47-6.04	5 (0.35)	0.15-0.82	97 (3.38%)	2.78-4.10	0 (0.00)	0.00-0.06	188 (1.37%)	1.19-1.58
Number of antibiotic courses for treatment of COPD exacerbations/LRTI in the year prior to index date												
0	1,625 (75.27)	73.40-77.04	639 (62.34)	59.33-65.26	1,218 (85.53)	83.61-87.27	1,404 (48.87%)	47.04-50.70	5,185 (83.28)	82.33-84.19	10,071 (73.47%)	72.73-74.21
1	293 (13.57)	12.19-15.08	204 (19.90)	17.57-22.46	114 (8.01)	6.71-9.53	640 (22.28%)	20.79-23.83	745 (11.97)	11.18-12.80	1,996 (14.56%)	13.98-15.16
2	123 (5.70)	4.80-6.76	96 (9.37)	7.73-11.30	48 (3.37)	2.55-4.44	364 (12.67%)	11.50-13.94	217 (3.49)	3.06-3.97	848 (6.19%)	5.80-6.60
3 or more	118 (5.47)	4.58-6.51	86 (8.39)	6.84-10.25	44 (3.09)	2.31-4.12	465 (16.19%)	14.88-17.58	79 (1.27)	1.02-1.58	792 (5.78%)	5.40-6.18

Characteristic	**THIN [UK] (N=2,159)**		**IPCI [NL] (N=1,025)**		**Aarhus [DK] (N=1,424)**		**HSD [IT] (N=2,873)**		**SIDIAP [ES] (N=6,226)**		**Pooled Data (N=13,707)**	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	95% CI
Duration of COPD (years)												
Mean (SD)	5.96 (5.98)		6.79 (5.83)		5.76 (5.25)		5.79 (4.54)		6.14 (5.69)		6.33 (5.50)	
Median (IQR)	4.54 (1.19-8.77)		5.80 (2.26-9.56)		4.30 (1.17-8.92)		5.54 (1.16-9.5)		4.87 (1.59-9.15)		5.34 (1.92-9.36)	
Min-max	0-43.55		0-37.84		0-20.3		0-14.83		0-44.5		0-44.5	

*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 16-3 Prescribed dosage of NVA237 assessed at index date and number of patients who used NVA237 for more than one year – by calendar year and pooled

Prescribed dosage	2012 (N=72)		2013 (N=6,384)		2014 (N=7,148)		2015 (N=103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Prescribed dosage of NVA237 at index date								
once daily	n.a.		2,617 (98.46)	97.91-98.86	3,200 (98.13)	97.6-98.54	103 (100.0)	96.40-100.0
every other day	n.a.		21 (0.79)	0.52-1.2	22 (0.67)	0.45-1.02	n.a.	
twice daily	n.a.		20 (0.75)	0.49-1.16	39 (1.2)	0.88-1.63	n.a.	
other	n.a.		1 (0.04)	0.01-0.21	n.a.		n.a.	
Information on dose missing	72 (100.0)	94.93-100.00	3,765 (58.98)	57.76-60.18	3,887 (54.38)	53.22-55.53	n.a.	
Median duration of NVA237 (days)(min-max)	138.50 (19-765)		90.00 (3-749)		60 (1-416)		16 (1-32)	
Number of patients who use NVA237 for more than 1 year (without interruption)	20 (27.78)	18.76-39.05	1,219 (19.09)	18.15-20.08	22 (0.31)	0.20- 0.47	0 (0.00)	0.00- 3.60

CI=Confidence interval;

Table 16-4 Indication for NVA237-initiation, as assessed at index date (based on indication found in the patients' medication prescription or medical files) – by calendar year

Indication of use	2012 (N=72)		2013 (N=6,384)		2014 (N=7,148)		2015 (N=103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
COPD#	38 (95.00)	83.50-98.62	4,257 (75.55)	74.41-76.65	4,695 (74.39)	73.3-75.46	78 (78.79)	69.74-85.69
Asthma#	0 (0.00)	0.00-8.76	439 (7.79)	7.12-8.52	565 (8.95)	8.27-9.68	3 (3.03)	1.04-8.53
Asthma and COPD#	2 (5.00)	1.38-16.5	653 (11.59)	10.78-12.45	594 (9.41)	8.72-10.16	17 (17.17)	11.01-25.79
Other#	0 (0.00)	0.00-8.76	286 (5.08)	4.53-5.68	457 (7.24)	6.63-7.91	1 (1.01)	0.18-5.5
Indication of use unknown	32 (44.44)	33.54-55.91	749 (11.73)	10.97-12.54	837 (11.71)	10.98-12.48	4 (3.88)	1.52-9.56
Potential off-label use*	0 (0.00)	0.00-8.76	725 (12.87)	12.02-13.77	1,026 (16.26)	15.37-17.19	4 (4.04)	1.58-9.93

*Potential off label use is defined as the combination of the "Asthma" and "Other" categories, as per protocol. #Number of patients for whom indication of use is available as denominator; CI=confidence interval

Table 16-5 Description of disease codes registered at time of NVA237 prescription for patients where NVA237 is used for indications other than COPD, asthma, or COPD and asthma

Description	Numbers	Percentage
THIN (other indication) n=73		
Other	19	26.03%
Dyspnea	18	24.66%
Cough	14	19.18%
Resp Other	12	16.44%
Resp Infection	9	12.33%
Resp Failure	1	1.37%
IPCI (other indication) n=46		
Dyspnea	22	47.83%
Coughing	14	30.43%
Lungcancer	4	8.70%
Acute bronchitis	1	2.17%
Lungfibrosis	1	2.17%
Sarcoidosis	1	2.17%
Wheezing	1	2.17%
Sputum production	1	2.17%
Upper respiratory tract infection	1	2.17%
Aarhus (other indication) n=16		
Pneumonia	5	31.25%
Bronchiectasis	4	25.00%
Chronic Sinusitis	2	12.50%
Respiratory Failure	2	12.50%
Interstitial Pulmonary Disease	1	6.25%

Description	Numbers	Percentage
Other Respiratory Disease	1	6.25%
Pleural Effusion	1	6.25%
HSD (other indication) n=229		
Acute Bronchitis	44	19.21%
Acute Respiratory Failure	21	9.17%
Cough	21	9.17%
Dyspnea	21	9.17%
Other Respiratory Abnormalities	20	8.73%
Lungcancer	19	8.30%
Pneumonia	10	4.37%
Bronchiectasis	8	3.49%
Heartfailure	8	3.49%
Chronic Respiratory Conditions	7	3.06%
Other	5	2.18%
Upper Respiratory Tract Infections	5	2.18%
Acute Tracheitis	4	1.75%
No Indication Mentioned	4	1.75%
Sleep Apnea	4	1.75%
Pneumothorax	3	1.31%
Sarcoidosis	3	1.31%
Allergic Rhinitis	2	0.87%
Allergy	2	0.87%
Hemoptysis	2	0.87%
Other Chronic Pulmonary Diseases	2	0.87%
Voice Disorders	2	0.87%
Chest Pain	1	0.44%
Chronic Rhinitis	1	0.44%

Description	Numbers	Percentage
Empyema	1	0.44%
Ischemic Heart Disease	1	0.44%
Pleurisy	1	0.44%
Pneumoconiosis	1	0.44%
Pulmonary Collapse	1	0.44%
Pulmonary Effusion	1	0.44%
Pulmonary Embolism	1	0.44%
Pulmonary Hypertension	1	0.44%
Rib fracture	1	0.44%
Wegener's Granulomatosis	1	0.44%
SIDIAP (other indication) n= 380		
Lower Respiratory Tract Infections	180	47.37%
Respiratory Other	66	17.37%
Upper Respiratory Tract Infections	59	15.53%
Dyspnea	31	8.16%
Cough	28	7.37%
Respiratory Failure	5	1.32%
Allergic Rhinitis	4	1.05%
Influenza	2	0.53%
Wheezing	2	0.53%
Disorder Sinus	1	0.26%
Disorder Vocal Cords	1	0.26%
Rhinitis	1	0.26%

Table 16-6 Cardiovascular and cerebrovascular co-morbidities (selected items) – by database and pooled

Comorbidity	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Cerebrovascular events:												
Stroke	182 (8.43)	7.33-9.68	60 (5.85)	4.57-7.46	68 (4.78)	3.78-6.01	310 (10.79)	9.71-11.98	311 (5.00)	4.48-5.56	931 (6.79)	6.38-7.23
TIA	112 (5.19)	4.33-6.21	51 (4.98)	3.80-6.48	34 (2.39)	1.71-3.32	98 (3.41)	2.81-4.14	125 (2.01)	1.69-2.39	420 (3.06)	2.79-3.37
Cardiovascular events:												
Ischemic Heart disease*:	406 (18.81%)	17.21-20.51	207 (20.20%)	17.85-22.76	280 (19.66%)	17.68-21.81	212 (7.38%)	6.48-8.39	471 (7.57%)	6.93-8.25	1,576 (11.50%)	10.97-12.04
Myocardial infarction	155 (7.18)	6.16-8.35	91 (8.88)	7.29-10.78	110 (7.72)	6.45-9.23	130 (4.52)	3.82-5.35	311 (5.00)	4.48-5.56	797 (5.81)	5.44-6.22
Angina pectoris	360 (16.67)	15.16-18.31	134 (13.07)	11.15-15.28	230 (16.15)	14.33-18.15	87 (3.03)	2.46-3.72	198 (3.18)	2.77-3.65	1,009 (7.36)	6.94-7.81
Unstable angina pectoris	47 (2.18)	1.64-2.88	19 (1.85)	1.19-2.88	47 (3.30)	2.49-4.36	16 (0.56)	0.34-0.90	45 (0.72)	0.54-0.97	174 (1.27)	1.10-1.47
Unstable ischemic heart disease	180 (8.34)	7.24-9.58	104 (10.15)	8.44-12.15	143 (10.04)	8.59-11.71	144 (5.01)	4.27-5.87	341 (5.48)	4.94-6.07	912 (6.65)	6.25-7.08
Heart failure	170 (7.87)	6.81-9.09	146 (14.24)	12.24-16.52	101 (7.09)	5.87-8.54	265 (9.22)	8.22-10.34	570 (9.16)	8.46-9.90	1,252 (9.13)	8.66-9.63
Cardiac arrhythmia#:	202 (9.36)	8.20-10.66	120 (11.71)	9.88-13.82	162 (11.38)	9.83-13.13	368 (12.81)	11.64-14.08	724 (11.63)	10.86-12.45	1,576 (11.50)	10.97-12.04
AV block	10 (0.46)	0.25-0.85	6 (0.59)	0.27-1.27	20 (1.40)	0.91-2.16	34 (1.18)	0.85-1.65	131 (2.10)	1.78-2.49	201 (1.47)	1.28-1.68
Atrial flutter/fibrillation	191 (8.85)	7.72-10.12	108 (10.54)	8.80-12.57	152 (10.67)	9.17-12.39	347 (12.08)	10.94-13.32	607 (9.75)	9.04-10.51	1,405 (10.25)	9.75-10.77

Comorbidity	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Ventricular tachycardia	5 (0.23)	0.10-0.54	5 (0.49)	0.21-1.14	3 (0.21)	0.07-0.62	2 (0.07)	0.02-0.25	15 (0.24)	0.15-0.40	30 (0.22)	0.15-0.31
Ventricular fibrillation	2 (0.09)	0.03-0.34	6 (0.59)	0.27-1.27	1 (0.07)	0.01-0.40	2 (0.07)	0.02-0.25	2 (0.03)	0.01-0.12	13 (0.09)	0.06-0.16
Torsade de Pointes/Long QT syndrome	1 (0.05)	0.01-0.26	1 (0.10)	0.02-0.55	0 (0.00)	0.00-0.27	1 (0.03)	0.01-0.20	0 (0.00)	0.00-0.06	3 (0.02)	0.01-0.06

*Ischemic heart disease consisting of (unstable) angina pectoris or myocardial infarction; # Cardiac arrhythmia consisting of AV block, atrial flutter/fibrillation, ventricular tachycardia, ventricular fibrillation or Torsade de Pointes/Long QT syndrome; TIA=Transient ischemic attack; AV=Atrioventricular; CI=confidence interval

Table 16-7 Cardiovascular and cerebrovascular co-morbidities (selected items) – by calendar year

Comorbidity	2012 (N=72)		2013 (N=6,384)		2014 (N=7,148)		2015 (N=103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Cerebrovascular events:								
Stroke	4 (5.56)	2.18-13.43	384 (6.02%)	5.46- 6.63	537 (7.51%)	6.92- 8.15	6 (5.83)	2.70-12.13
TIA	3 (4.17)	1.43-11.55	192 (3.01)	2.62- 3.46	219 (3.06)	2.69- 3.49	6 (5.83)	2.70-12.13
Cardiovascular events:								
Ischemic Heart disease:								
Myocardial infarction	4 (5.56)	2.18-13.43	405 (6.34)	5.77- 6.97	381 (5.33)	4.83- 5.88	7 (6.80)	3.33-13.37
Angina pectoris	6 (8.33)	3.88-17.01	512 (8.02)	7.38- 8.71	479 (6.70)	6.14- 7.30	12 (11.65)	6.79-19.27
Unstable angina pectoris	3 (4.17)	1.43-11.55	85 (1.33)	1.08- 1.64	85 (1.19)	0.96- 1.47	1 (0.97)	0.17- 5.30
Unstable ischemic heart disease*	7 (9.72)	4.79-18.74	456 (7.14)	6.54- 7.80	442 (6.18)	5.65- 6.77	7 (6.80)	3.33-13.37
Heart failure	6 (8.33)	3.88-17.01	564 (8.83)	8.16- 9.56	674 (9.43)	8.77-10.13	8 (7.77)	3.99-14.58
Cardiac arrhythmia:								
AV block	0 (0.00)	0.00- 5.07	102 (1.60)	1.32- 1.94	98 (1.37)	1.13- 1.67	1 (0.97)	0.17- 5.30
Atrial flutter/fibrillation	8 (11.11)	5.74-20.42	636 (9.96)	9.25-10.72	749 (10.48)	9.79-11.21	12 (11.65)	6.79-19.27
Ventricular tachycardia	0 (0.00)	0.00- 5.07	14 (0.22)	0.13- 0.37	16 (0.22)	0.14- 0.36	0 (0.00)	0.00- 3.60
Ventricular fibrillation	1 (1.39)	0.25- 7.46	7 (0.11)	0.05- 0.23	4 (0.06)	0.02- 0.14	1 (0.97)	0.17- 5.30
Torsade de Pointes/Long QT synd.	0 (0.00)	0.00- 5.07	2 (0.03)	0.01- 0.11	1 (0.01)	0.00- 0.08	0 (0.00)	0.00- 3.60

*myocardial infarction or unstable angina pectoris; TIA=Transient ischemic attack; AV=Atrioventricular; CI=confidence interval

Table 16-8 Underlying conditions corresponding to population defined in the "Missing information section" of the RMP or who have high risk treatment conditions – by calendar year

Underlying condition	2012 (N= 72)		2013 (N= 6,384)		2014 (N= 7,148)		2015 (N= 103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Unstable isch. heart disease*	7 (9.72)	4.79-18.74	456 (7.14)	6.54- 7.80	442 (6.18)	5.65- 6.77	7 (6.80)	3.33-13.37
LongQT synd./Torsade de Pointes	0 (0.00)	0.00- 5.07	2 (0.03)	0.01- 0.11	1 (0.01)	0.00- 0.08	0 (0.00)	0.00- 3.60
Cardiac arrhythmia**	8 (11.11)	5.74-20.42	724 (11.34)	10.59-12.14	830 (11.61)	10.89-12.38	14 (13.59)	8.27-21.53
Urinary retention or sympt. bladder outflow obstruction	1 (1.39)	0.25- 7.46	82 (1.28)	1.04- 1.59	111 (1.55)	1.29- 1.87	6 (5.83)	2.70-12.13
Narrow-angle glaucoma	0 (0.00%)	0.00- 5.07	8 (0.13%)	0.06- 0.25	7 (0.10%)	0.05- 0.20	0 (0.00%)	0.00- 3.60
Renal impairment (CKD stages)***								
Stage 1 (kidney damage with eGFR>= 90 mL/min/1.73m^2)****	0 (0)	0-5.07	79 (1.24)	0.99- 1.54	145 (2.03)	1.73- 2.38	0 (0)	0-3.6
Stage 2 (eGFR 60-89 mL/min/1.73m^2)	36 (50.00)	38.75-61.25	2,878 (45.08)	43.86-46.30	3,222 (45.08)	43.92-46.23	49 (47.57)	38.19-57.13
Stage 3 (eGFR 30-59 mL/min/1.73m^2)	13 (18.06)	10.87-28.48	1,281 (20.07)	19.10-21.07	1,540 (21.54)	20.61-22.51	25 (24.27)	17.01-33.38
Stage 4 (eGFR 15-29 mL/min/1.73m^2)	0 (0)	0-5.07	146 (2.29)	1.95- 2.68	138 (1.93)	1.64- 2.28	3 (2.91)	1.00- 8.22
Stage 5 (eGFR< 15 mL/min/1.73m^2 or dialysis)	0 (0)	0-5.07	22 (0.34)	0.23- 0.52	49 (0.69)	0.52- 0.91	2 (1.94)	0.53- 6.81
CKD missing (no serum creatinine levels)	0 (0)	0-5.07	87 (1.36)	1.11- 1.68	87 (1.22)	0.99- 1.50	1 (0.97)	0.17- 5.30

Underlying condition	2012 (N= 72)		2013 (N= 6,384)		2014 (N= 7,148)		2015 (N= 103)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
No CKD*****	23 (31.94)	22.33-43.39	1,891 (29.62)	28.51-30.75	1,967 (27.52)	26.50-28.57	23 (22.33)	15.37-31.28
Liver disease	0 (0.00)	0.00- 5.07	144 (2.26)	1.92- 2.65	189 (2.64)	2.30- 3.04	4 (3.88)	1.52- 9.56
Pregnancy within 9 months prior to treatment start	0 (0.00)	0.00- 5.07	1 (0.02)	0.00- 0.09	0 (0.00)	0.00- 0.05	0 (0.00)	0.00- 3.60
Pregnancy during NVA237	0 (0.00)	0.00- 5.07	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.05	0 (0.00)	0.00- 3.60
Breastfeeding recorded within 12 mths prior to NVA237 start	0 (0.00)	0.00- 5.07	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.05	0 (0.00)	0.00- 3.60
Breastfeeding during NVA237	0 (0.00)	0.00- 5.07	0 (0.00)	0.00- 0.06	0 (0.00)	0.00- 0.05	0 (0.00)	0.00- 3.60

*myocardial infarction and unstable angina pectoris; **any diagnosis of atrioventricular block, atrial flutter/fibrillation, ventricular tachycardia/fibrillation, Torsade de Pointes/QTc prolongation; 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 ; CI=Confidence interval

Table 16-9 History of co-morbidities in patients initiating NVA2237 (assessed at index date and considering the complete medical history of the patients)

Comorbidity	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Cardiovascular co-morbidities												
Angina pectoris	360 (16.67)	15.16-18.31	134 (13.07)	11.15-15.28	230 (16.15)	14.33-18.15	87 (3.03)	2.46-3.72	198 (3.18)	2.77-3.65	1,009 (7.36)	6.94-7.81
Unstable angina pectoris	47 (2.18)	1.64-2.88	19 (1.85)	1.19-2.88	47 (3.30)	2.49-4.36	16 (0.56)	0.34-0.90	45 (0.72)	0.54-0.97	174 (1.27)	1.10-1.47
Myocardial infarction	155 (7.18)	6.16-8.35	91 (8.88)	7.29-10.78	110 (7.72)	6.45-9.23	130 (4.52)	3.82-5.35	311 (5.00)	4.48-5.56	797 (5.81)	5.44-6.22
Heart failure	170 (7.87)	6.81-9.09	146 (14.24)	12.24-16.52	101 (7.09)	5.87-8.54	265 (9.22)	8.22-10.34	570 (9.16)	8.46-9.90	1,252 (9.13)	8.66-9.63
Cardiac arrhythmia												
All Cardiac arrhythmia combined	233 (10.79)	9.55-12.17	141 (13.76)	11.78-16.00	193 (13.55)	11.87-15.43	490 (17.06)	15.72-18.47	831 (13.35)	12.53-14.21	1,888 (13.77)	13.21-14.36
Atrial fibrillation/flutter	191 (8.85)	7.72-10.12	108 (10.54)	8.80-12.57	152 (10.67)	9.17-12.39	347 (12.08)	10.94-13.32	607 (9.75)	9.04-10.51	1,405 (10.25)	9.75-10.77
AV block	10 (0.46)	0.25-0.85	6 (0.59)	0.27-1.27	20 (1.40)	0.91-2.16	34 (1.18)	0.85-1.65	131 (2.10)	1.78-2.49	201 (1.47)	1.28-1.68
Torsade de Pointes/Long QTc	1 (0.05)	0.01-0.26	1 (0.10)	0.02-0.55	0 (0.00)	0.00-0.27	1 (0.03)	0.01-0.20	0 (0.00)	0.00-0.06	3 (0.02)	0.01-0.06
Ventricular fibrillation	2 (0.09)	0.03-0.34	6 (0.59)	0.27-1.27	1 (0.07)	0.01-0.40	2 (0.07)	0.02-0.25	2 (0.03)	0.01-0.12	13 (0.09)	0.06-0.16

Comorbidity	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Ventricular tachycardia	5 (0.23)	0.10-0.54	5 (0.49)	0.21-1.14	3 (0.21)	0.07-0.62	2 (0.07)	0.02-0.25	15 (0.24)	0.15-0.40	30 (0.22)	0.15-0.31
Premature depolarization	20 (0.93)	0.60-1.43	17 (1.66)	1.04-2.64	13 (0.91)	0.53-1.56	129 (4.49)	3.79-5.31	64 (1.03)	0.81-1.31	243 (1.77)	1.57-2.01
Sick sinus syndrome	1 (0.05)	0.01-0.26	2 (0.20)	0.05-0.71	20 (1.40)	0.91-2.16	22 (0.77)	0.51-1.16	1 (0.02)	0.00-0.09	46 (0.34)	0.25-0.45
Supraventricular tachycardia	27 (1.25)	0.86-1.81	9 (0.88)	0.46-1.66	42 (2.95)	2.19-3.96	22 (0.77)	0.51-1.16	62 (1.00)	0.78-1.27	162 (1.18)	1.01-1.38
Cerebrovascular co-morbidities												
Stroke	182 (8.43)	7.33-9.68	60 (5.85)	4.57-7.46	68 (4.78)	3.78-6.01	310 (10.79)	9.71-11.98	311 (5.00)	4.48-5.56	931(6.79)	6.38-7.23
TIA	112 (5.19)	4.33-6.21	51 (4.98)	3.80-6.48	34 (2.39)	1.71-3.32	98 (3.41)	2.81-4.14	125 (2.01)	1.69-2.39	420 (3.06)	2.79-3.37
Other comorbidities												
Hepatic impairment	95 (4.40)	3.61-5.35	27 (2.63)	1.82-3.81	15 (1.05)	0.64-1.73	164 (5.71)	4.92-6.62	36 (0.58)	0.42-0.80	337 (2.46)	2.21-2.73
Narrow angle glaucoma	100 (4.63)	3.82-5.60	27 (2.63)	1.82-3.81	36 (2.53)	1.83-3.48	241 (8.39)	7.43-9.46	399 (6.41)	5.83-7.04	803 (5.86)	5.48-6.26
Other glaucoma	98 (4.54%)	3.74-5.50	27 (2.63%)	1.82-3.81	36 (2.53%)	1.83-3.48	240 (8.35%)	7.40-9.42	398 (6.39%)	5.81-7.03	799 (5.83%)	5.45-6.23
Urinary retention or bladder outflow symptoms	75 (3.47)	2.78-4.33	16 (1.56)	0.96-2.52	18 (1.26)	0.80-1.99	22 (0.77)	0.51-1.16	69 (1.11)	0.88-1.40	200 (1.46)	1.27-1.67
BPH	114 (5.28)	4.41-6.31	77 (7.51)	6.05-9.29	81 (5.69)	4.60-7.01	422 (14.69)	13.44-16.03	1,195 (19.19)	18.23-20.19	1,889 (13.78)	13.21-14.37

Comorbidity	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Chronic kidney disease (CKD)*												
Stage 1 (kidney damage with eGFR>= 90 mL/min/1.73m^2)**	2 (0.09)	0.03-0.34	0 (0.00)	0-0.37	0 (0.00)	0-0.27	222 (7.73)	6.81-8.76	0 (0.00)	0.00-0.06	224 (1.63)	1.44-1.86
Stage 2 (eGFR 60-89 mL/min/1.73m^2)	1048 (48.54)	46.44-50.65	475 (46.34)	43.31-49.40	686 (48.17)	45.59-50.77	1,090 (37.94)	36.18-39.73	2,886 (46.35)	45.12-47.59	6,185 (45.12)	44.29-45.96
Stage 3 (eGFR 30-59 mL/min/1.73m^2)	652 (30.20)	28.30-32.17	119 (11.61)	9.79-13.72	215 (15.10)	13.33-17.05	923 (32.13)	30.44-33.86	950 (15.26)	14.39-16.17	2,859 (20.86)	20.19-21.55
Stage 4 (eGFR 15-29 mL/min/1.73m^2)	63 (2.92)	2.29-3.72	8 (0.78)	0.40-1.53	21 (1.47)	0.97-2.24	125 (4.35)	3.66-5.16	70 (1.12)	0.89-1.42	287 (2.09)	1.87-2.35
Stage 5 (eGFR< 15 mL/min/1.73m^{2}or dialysis)	5 (0.23)	0.10-0.54	0 (0.00)	0.00-0.37	2 (0.14)	0.04-0.51	59 (2.05)	1.60-2.64	7 (0.11)	0.05-0.23	73 (0.53)	0.42-0.67
CKD stage unknown (no serum creatinine levels)	23 (1.07)	0.71-1.59	23 (2.24)	1.50-3.34	4 (0.28)	0.11-0.72	8 (0.28)	0.14-0.55	117 (1.88)	1.57-2.25	175 (1.28)	1.10-1.48
No CKD***	366 (16.95)	15.43-18.59	400 (39.02)	36.08-42.05	496 (34.83)	32.40-37.34	446 (15.52)	14.25-16.89	2,196 (35.27)	34.09-36.47	3,904 (28.48)	27.73-29.24

CKD=Chronic kidney disease; *CKD stage based on both disease codes and lab results. If both CKD stage based on disease codes and lab results were available, the CKD stage closest and most severe to the index date was considered; **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) ; CI=Confidence interval; BPH=Benign prostatic hyperplasia; TIA=Transient ischemic attack; AV=Atrioventricular

Table 16-10 Use of other respiratory medications (assessed in the six months prior to and including the index date)

Medication	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Singel-ingredient medications												
LABA	264 (12.23)	10.91-13.68	249 (24.29)	21.77-27.01	515 (36.17)	33.71-38.70	669 (23.29)	21.78-24.87	1,793 (28.80)	27.69-29.94	3,490 (25.46)	24.74-26.20
LAMA (other than NVA237)	860 (39.83)	37.79-41.91	373 (36.39)	33.50-39.38	409 (28.72)	26.43-31.13	701 (24.40)	22.86-26.00	1,479 (23.76)	22.71-24.83	3,822 (27.88)	27.14-28.64
SAMA	186 (8.62)	7.50-9.87	162 (15.80)	13.70-18.17	10 (0.70)	0.38-1.29	135 (4.70)	3.98- 5.54	1,756 (28.20)	27.10-29.34	2,249 (16.41)	15.80-17.04
SABA	1861 (86.20)	84.68-87.59	422 (41.17)	38.20-44.21	660 (46.35)	43.77-48.94	385 (13.40)	12.20-14.70	2,285 (36.70)	35.51-37.91	5,613 (40.95)	40.13-41.78
ICS	274 (12.69)	11.35-14.16	188 (18.34)	16.09-20.83	206 (14.47)	12.73-16.39	818 (28.47)	26.85-30.15	1,263 (20.29)	19.31-21.30	2,749 (20.06)	19.39-20.73
Xanthines	118 (5.47)	4.58-6.51	26 (2.54)	1.74-3.69	14 (0.98)	0.59-1.64	261 (9.08)	8.09-10.19	132 (2.12)	1.79-2.51	551 (4.02)	3.70-4.36
Fixed-combination medications												
LABA+ICS	1,277 (59.15)	57.06-61.20	540 (52.68)	49.62-55.72	556 (39.04)	36.54-41.61	1,261 (43.89)	42.09-45.71	2,706 (43.46)	42.24-44.70	6,340 (46.25)	45.42-47.09

Medication	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
SABA+ SAMA	8 (0.37)	0.19- 0.73	67 (6.54)	5.18- 8.22	77 (5.41)	4.35- 6.71	324 (11.28)	10.17- 12.49	22 (0.35)	0.23- 0.53	498 (3.63)	3.33- 3.96
LABA+LAMA	0 (0.00)	0.00- 0.18	5 (0.49)	0.21- 1.14	15 (1.05)	0.64- 1.73	0 (0.00)	0.00- 0.13	25 (0.40)	0.27- 0.59	45 (0.33)	0.25- 0.44
Other respiratory medications												
Oral ß$_2$-agonists	5 (0.23)	0.10- 0.54	0 (0.00)	0.00- 0.37	14 (0.98)	0.59- 1.64	1 (0.03)	0.01- 0.20	23 (0.37)	0.25- 0.55	43 (0.31)	0.23- 0.42
LTRA	70 (3.24)	2.57- 4.08	57 (5.56)	4.32- 7.14	49 (3.44)	2.61- 4.52	122 (4.25)	3.57- 5.05	387 (6.22)	5.64- 6.84	685 (5.00)	4.65- 5.37
Systemic corticosteroids (overall)	936 (43.35)	41.28- 45.45	433 (42.24)	39.25- 45.29	390 (27.39)	25.13- 29.76	933 (32.47)	30.79- 34.21	1673 (26.87)	25.78- 27.99	4,365 (31.85)	31.07- 32.63
Systemic corticosteroids – indication COPD	349 (16.16)	14.67- 17.78	243 (23.71)	21.20- 26.41	127 (8.92)	7.55- 10.51	512 (17.82%)	16.46- 19.26	198 (3.18)	2.77- 3.65	1429 (10.43%)	9.92- 10.95
Oral PDE-4 inhibitors	2 (0.09)	0.03- 0.34	0 (0.00)	0.00- 0.37	2 (0.14)	0.04- 0.51	7 (0.24)	0.12- 0.50	103 (1.65)	1.37- 2.00	114 (0.83)	0.69- 1.00

SAMA= short-acting muscarinic agents, SABA= short-acting β_2-agonists, ICS= inhaled corticosteroids, LTRA=Leukotriene receptor antagonists, LABA= Long acting β_2-agonists, LAMA= long-acting muscarinic agents; PDE=Phosphodiesterase; CI=Confidence interval

Table 16-11 Use of systemic anticholinergic medications (assessed in the six months prior to the index date (including prescriptions on index date)) – by database and pooled

Systemic anticholinergic	THIN [UK] (N=2,159)		IPCI [NL] (N=1,025)		Aarhus [DK] (N=1,424)		HSD [IT] (N=2,873)		SIDIAP [ES] (N=6,226)		Pooled Data (N=13,707)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Antipsychotic medications	132 (6.11)	5.18-7.20	31 (3.02)	2.14-4.26	76 (5.34)	4.29-6.63	67 (2.33)	1.84-2.95	300 (4.82)	4.31-5.38	606 (4.42)	4.09-4.78
Antidepressant agents (tricyclic and tetracyclic)	337 (15.61)	14.14-17.20	70 (6.83)	5.44-8.54	161 (11.31)	9.76-13.06	160 (5.57)	4.79-6.47	515 (8.27)	7.61-8.98	1243 (9.07)	8.60-9.56
Disopyramide	0 (0.00)	0.00-0.18	1 (0.10)	0.02-0.55	0 (0.00)	0.00-0.27	0 (0.00)	0.00-0.13	0 (0.00)	0.00-0.06	1 (0.01)	0.00-0.04
Antispasmodics	61 (2.83)	2.21-3.61	17 (1.66)	1.04-2.64	1 (0.07)	0.01-0.40	14 (0.49)	0.29-0.82	37 (0.59)	0.43-0.82	130 (0.95)	0.80-1.12
Antiparkinson medications	7 (0.32)	0.16-0.67	3 (0.29)	0.10-0.86	1 (0.07)	0.01-0.40	3 (0.10)	0.04-0.31	13 (0.21)	0.12-0.36	27 (0.20)	0.14-0.29
Cholinesterase inhibitors	2 (0.09)	0.03-0.34	0 (0.00)	0.00-0.37	0 (0.00)	0.00-0.27	3 (0.10)	0.04-0.31	13 (0.21)	0.12-0.36	18 (0.13)	0.08-0.21
Atropine	0 (0.00)	0.00-0.18	0 (0.00)	0.00-0.37	0 (0.00)	0.00-0.27	0 (0.00)	0.00-0.13	0 (0.00)	0.00-0.06	0 (0.00)	0.00-0.03
H1-antihistaminics	265 (12.27)	10.96-13.73	115 (11.22)	9.43-13.30	71 (4.99)	3.97-6.24	262 (9.12)	8.12-10.23	934 (15.00)	14.14-15.91	1,647 (12.02)	11.48-12.57
Anticholinergics for treatment of overactive bladder	86 (3.98)	3.24-4.89	20 (1.95)	1.27-2.99	22 (1.54)	1.02-2.33	20 (0.70)	0.45-1.07	179 (2.88)	2.49-3.32	327 (2.39)	2.14-2.65

CI=Confidence interval

Annex 2.2 – Comorbidity definitions

1. 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.

2. Angina pectoris

According to the guidelines of the European Heart Association; angina pectoris is described as chest discomfort due to myocardial ischemia 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	
Ischemic 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				

Terms	ICD10	ICD9CM	Read Codes	ICPC
			G311500	
			G33z000	
Angina at rest			G311.14	
			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 ischemic heart disease			G34..	

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

3. Myocardial infarction

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			

Terms	ICD10	ICD9CM	Read Codes	ICPC
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.]	
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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

4. Heart failure (HF)

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	I13.2	404.01		

Terms	ICD10	ICD9CM	Read Codes	ICPC
failure		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	
			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

5. 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	
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
			G6X..00/Gyu6G00	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*		
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
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

6. Transient ischemic attack (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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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

7. Cardiac arrhythmia

Atrial flutter (AFL) 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	
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) 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			

Terms	ICD10	ICD9CM	Read Codes	ICPC
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 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 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 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) 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	426.82	X202	

Terms	ICD10	ICD9CM	Read Codes	ICPC
	147.2E			
ECG: Q-T interval prolonged			32K3.00	

Supraventricular tachycardia (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
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 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 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.	
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 G5610	K84.02
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 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 I49.40 I49.49	427.6	G576z00 G576011	K80
Supraventricular extrasystole		427.61	G576100	K80.01
Ventricular extrasystole	I49.3		G576500 G576200	K80.02
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	

Terms	ICD10	ICD9CM	Read codes	ICPC
ECG: atrial ectopics			3264.00	
ECG: ectopic beats NOS			326Z.00	
Ectopic beats			G576.00	
Premature beats			G576.11	
Ectopic beats unspecified			G576000	

8. Definition of 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	

9. Definition of chronic kidney disease (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
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
			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..	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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:

$$GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

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.

10. Definition of hepatic impairment

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 medications. 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	794.8	44G2.	
	R74		R148.	
			44D2.	
			44G3100	
			44G4100	
			44H5100	
			44H5200	
			R148.00	
Hepatic failure, unspecified	K72.9			
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	

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

11. Definition of lower respiratory tract infection (LRTI) (indication of use of antibiotics)

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	

12. Glaucoma (narrow-angle glaucoma and other)

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	
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	

13. Bladder obstruction/urinary retention/benign prostatic hyperplasia (BPH)

Definition of bladder obstruction/urinary retention

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 (Verhamme et al 2008).

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	
BOO - Bladder outflow obstruction			K160.13	
Bladder outflow obstruction			K165200	
Bladder neck obstruction	N32.0	596.0		

Definition of BPH

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 over activity is thought to be a contributor to the storage symptoms seen in LUTS (Juliao et al 2012).

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

14. Pregnancy and breast feeding

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...	W78
		ZV..	W79
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

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

Annex 2.3 – Exposure definition – NVA237 and other respiratory medication use

Medication	ATC code
NVA237	R03BB06

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

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	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
	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

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
	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 medications for obstructive airway diseases	no	no		no	no
	R03AK02	Isoprenaline and other medications 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
	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

Class of medication	ATC code	Description	UK	NL	DK	IT	SP
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
	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 (GOLD 2016).

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 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:

I. Mild COPD (GOLD stage I): $FEV_1/FVC<70\%$ and FEV_1 predicted > 80%
II. Moderate COPD (GOLD stage II): $FEV_1/FVC<70\%$ and $50\%<FEV_1\leq80\%$ predicted
III. Severe COPD (GOLD stage III): $FEV_1/FVC<70\%$ and $30\%<FEV_1\leq50\%$ predicted
IV. Very severe COPD (GOLD stage IV): $FEV_1/FVC<70\%$ and $FEV_1\leq30\%$ predicted or $FEV_1<50\%$ predicted and chronic respiratory failure.

The most recently performed spirometry prior to the index date 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]) (GOLD 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 will be considered.

1. Mild: Patients initially diagnosed with COPD
2. Moderate: Patients on regular treatment (defined as at least 2 prescriptions of the same medication group within 6 months) with inhaled bronchodilators, xanthines or combination therapy. Patients are considered to have moderate COPD from the time of the second prescription on.
3. 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)
4. Very severe: Patients requiring chronic oxygen therapy.
5.

Annex 2.5 – COPD, chronic bronchitis and emphysema as indication of use of NVA237, and 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 NVA237. 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
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 medications

Antipsychotic medications **(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 medications

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 Medications, 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, medication dispensing and actual medication 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 medication 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 and Larsen 1994).

Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according the dosing regimens of the respective Summary of Product Characteristics of the other medications. 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 medications, OTC medications or medications 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). Medication 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 NVA237 and according to the dosing regimens of the respective SmPC for the other medications. 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).