NON-INTERVENTIONAL (NI) STUDY PROTOCOL

POST-AUTHORISATION SAFETY STUDY (PASS) INFORMATION

Title	Post-Authorisation Safety Study (PASS) of the Utilisation Patterns of Apixaban in Denmark
Protocol number	B0661073
Protocol version identifier	Amendment 1
Date of last version of protocol	16 November 2015
European Union (EU) Post Authorisation Study (PAS) register number	Study not registered
Active substance	B01AF02/Apixaban
Medicinal product	ELIQUIS®
Product reference	EU/1/11/691/001-015
Procedure number	EMEA/H/C/002148
Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb/Pfizer European Economic Interest Grouping (EEIG).
Joint PASS	No
Research question and objectives	Specifically, the study seeks to: 1. Estimate the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study, 2. Describe the characteristics of the patients who are prescribed apixaban for on-label and off-label indications.
Country(-ies) of study	Denmark

Author	[redacted]

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH United Kingdom
MAH contact person	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical
BMS	Bristol-Myers Squibb
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Science
DCRS	Danish Civil Registration System
DNPR	Danish National Patient Register
DPA	Data Protection Agency
DVT	Deep Vein Thrombosis
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GEP	Good Epidemiology Practice
GPP	Good Pharmacoepidemiology Practices
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
MAH	Marketing Authorisation Holder
NHSPD	National Health Service Prescription Database
NOAC	Non-vitamin K Oral Anti-Coagulant
NOMESCO	Nordic Medico-Statistical Committee
NVAF	Nonvalvular Atrial Fibrillation
NYHA	New York Heart Association
PASS	Post-Authorisation Safety Study
PAS	Post-Authorisation Safety
PE	Pulmonary Embolism
SAP	Statistical Analysis Plan
SE	Systemic Embolism
SmPC	Summary of Product Characteristics
THR	Total Hip Replacement
TIA	Transient Ischaemic Attack
TKR	Total Knee Replacement
US	United States
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolism

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
[redacted]			

Country Coordinating Investigators

Not Applicable. The protocol only pertains to Denmark and Aarhus University.

3. ABSTRACT

Title: A Post-Authorisation Safety Study (PASS) of the Utilisation Pattern of Apixaban in Denmark

Rationale and background: Apixaban (ELIQUIS®) is an orally administered anticoagulant that was approved in the European Union (EU) in May 2011 for the prevention of venous thromboembolic events (VTE) in adults who have undergone elective hip or knee replacement surgery. Subsequently, apixaban received approvals for stroke and systemic embolism (SE) prevention in those with nonvalvular atrial fibrillation (NVAF), and for the treatment and prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) in adults. *Research question and objectives:* This study aims to estimate the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study, and describe the characteristics of the patients who are prescribed apixaban for on-label and off-label indications. *Study design:* These aims will be examined with a descriptive, retrospective, cross-sectional study that uses electronic healthcare data from the Danish national registries. *Population:* All patients dispensed apixaban as recorded in the Danish Health Services Prescription Database from May 2011 to December 2014 will be included. *Variables:* Data will be collected on apixaban dispensations, prescriber specialty, and patient characteristics such as age, gender, morbidities, concomitant medications, and hospital-based diagnoses and procedures. Patients will be classified as on-label or off-label users if their initial indication has been recorded or can be inferred from the registry data. If an apixaban indication is not present or cannot be inferred from the registries, the patients' indications will be considered unknown. *Data sources:* Information will be drawn from the Danish Civil Registration System (DCRS), Danish National Patient Register (DNPR), and the National Health Service Prescription Database (NHSPD). *Study Size:* The study will include approximately 8,000 patients who were dispensed apixaban during the study period. *Data analysis:* The proportion of those with on-label indications, and the characteristics of the on-label and off-label usage will be reported. *Milestones:* The study is anticipated to start on 31 August 2016 and the Final Study Report will be submitted approximately 1 year after the start of data collection.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	14 March 2016	Administrative	Abstract (3) Milestones (5) Variables (8.3) Data Sources (8.4) Data Management (8.6) Institutional Review Board (IRB) / Independent Ethics Committee (IEC) (9.3)	Dates of the milestones were amended. Updates and clarifications to names of Danish Registers. Clarification of SAS Version. Clarification on retaining correspondences and approvals from the Danish Data Protection Agency (DPA)	Dates were amended to align to EMA/PRAC review procedure. To clarify changes to current names of Registers. To update to versions of statistical software. To clarify procedures for retaining information from the DPA

5. MILESTONES

Milestone	Planned date*
Start of data collection	31 August 2016
End of data collection	30 November 2016
Registration in the EU PAS register	26 August 2016
Final study report	31 August 2017

*Data for the study come from electronic healthcare data that are collected by the governmental agencies and county health administrations in Denmark and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data by one or more of the agencies is beyond the control of the investigators and the Marketing Authorisation Holder (MAH). These delays may affect the study timeline and the date of the delivery of the final report.

6. RATIONALE AND BACKGROUND

Apixaban (ELIQUIS®) is a Non-vitamin K Oral Anti-Coagulant (NOAC) that inhibits the coagulation factor Xa. NOACs, which have become available in the last decade, provide an alternative to Vitamin K Antagonists (VKAs), which had been the mainstay of oral anticoagulation therapy for over a half century.[1,2] Patients and providers may choose NOACs because, compared to VKAs, NOACs have fewer food and drug interactions, a lower risk of bleeding for a similar anticoagulation effect, and a more predictable effect that allows patients to maintain an optimal therapeutic dose without frequent monitoring.[3]

In May 2011, apixaban was approved in the European Union (EU) for the prevention of venous thromboembolism (VTE) in adults undergoing total hip replacement (THR) or total knee replacement (TKR). Following the initial approval, apixaban received approvals, in November 2012, for the prevention of stroke and systemic embolism (SE) in adults with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, and then in July 2014, for treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (Table 1). The administration of apixaban for the approved indications will be considered 'on-label,' and any apixaban use that is inconsistent with the approved indications will be designated 'off-label' use.

Investigations into the off-label use of other NOACs, including dabigatran and rivaroxaban, have suggested varying frequencies of on-label and off-label use. For instance, in Denmark, national health registry data from 1612 dabigatran users were examined for off-label use between 22 August and 31 December 2011. Depending on a patient's risk factors for bleeding, dabigatran was indicated for NVAF at a high dose (150 mg) or low dose (110 mg). Dabigatran 150 mg was prescribed off-label in 44.5% of patients and dabigatran 110 mg was prescribed off-label in 9.7% patients.[4] In France, less than 1% of patients were classified as off-label because they received a NOAC and had a mechanical heart value.[5] In Belgium, however, 53.8% of dabigatran and rivaroxaban use were reported as off-label because the prescriptions had at least 1 inappropriate rating in a 10 category appropriate-use scale. Inappropriate dosing, particularly failing to adapt the NOAC dosing to the patient's renal function, was cited as a common off-label use.[6] In Wisconsin, United States (US), dabigatran was prescribed off-label to 20% of all patients receiving the drug including 10.9% of patients with valvular atrial fibrillation (AF) and 8.6% of patients with no identified AF diagnosis.[7] A second US study evaluated dabigatran utilisation with nationwide IMS Health data, and reported that 8% of dabigatran treatments were off-label in Quarter 4, 2010. However, by Quarter 4, 2011, the proportion of off-label prescriptions had increased to 37%.[8]

Apixaban was authorised for use in the EU after dabigatran became available. Currently little is known about the frequency of apixaban on-label and off-label use. To understand the pattern of post-authorisational apixaban use, the Marketing Authorisation Holder (MAH) initiated studies to evaluate the utilisation of apixaban in Sweden and the Netherlands, and proposes to complement those studies with a similar evaluation of apixaban utilisation in Denmark (described herein).

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

Table 1. Indications and Dates of EMA Authorisations

Name	Indication	Date of EMA Authorisation
THR/TKR	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.	18 May 2011
NVAF	Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age >= 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class >= II).	19 Nov 2012
Treatment of DVT/PE	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.	28 July 2014

DVT: Deep vein thrombosis
NVAF: Non-valvular atrial fibrillation
NYHA: New York Heart Association
PE: Pulmonary Embolism
SE: Systemic Embolism
TKR: Total Knee Replacement
THR: Total Hip Replacement
TIA: Transient Ischaemic Attack
VTE: Venous Thromboembolic Events

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the utilisation pattern of apixaban in Denmark with regard to on-label and off-label use.

Specifically, the study aims to:

1. Estimate the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study.

2. Describe the characteristics of the patients who are prescribed apixaban for on-label and off-label indications.

8. RESEARCH METHODS

8.1. Study Design

This is a descriptive, retrospective, cross-sectional study using electronic healthcare data from the Danish national registries. Apixaban patients will be identified through prescription registries, and medical histories will be assembled from the registration of hospital encounters. The patient's first apixaban prescription is compared to the medical history from prior to the prescription to determine if that patient received the medication for an on-label or off-label indication.

8.2. Setting

The study describes apixaban use from 18 May 2011 through 31 December 2014 in Denmark (population 5.6 million). Any patient receiving apixaban in Denmark recorded in routine outpatient dispensation records will be evaluated; there are no exclusion criteria for this study. Given the national extent of the Danish registries, the study population is expected to represent the population of Denmark accurately.

8.3. Variables

Data on apixaban dispensation, dose, and treatment duration will be collected. Patient data will be collected including the patients' gender, age, concomitant medications, hospital-based diagnoses and procedures, medical history including previous anticoagulant use, and morbidities such as cardiovascular, renal or hepatic disease. Additional data on the specialty of the prescriber will be ascertained.

Based on the patient's age, apixaban indication and the date of the dispensation, the indications will be classified as on-label, off-label, or unknown in instances where no indication can be inferred. The classification of the first prescription will define the patient's apixaban indication for the course of the study, and each apixaban patient will contribute a single observation to the study. Thus, patients who receive multiple prescriptions for apixaban will be classified as on-label, off-label, or unknown based on the first of those prescriptions. Patients who receive apixaban before 18 years of age, but who become 18 years old during the study will be considered off-label users because their first prescription was for an off-label indication. For indications that were approved during the study, only patients who received apixaban after the indication was approved will be classified as on-label. Patients who received prescriptions on or before the date of the new indication's approval will be designated off-label users. Patient records will be searched in the following order for:

1. Age, 18 years or older,

2. VTE prevention following *elective* THR/TKR (ie, THR/TKR without evidence of hip or knee fracture),

3. NVAF, which is defined as, 'AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis', according to the European Heart Rhythm Association[3] (on-label after approval on 19 November 2012),

4. DVT/PE treatment and prevention (on-label after approval on 28 July 2014),

5. Any other conditions from a list of pre-defined off-label indications, including other types of surgery and history of other diseases:

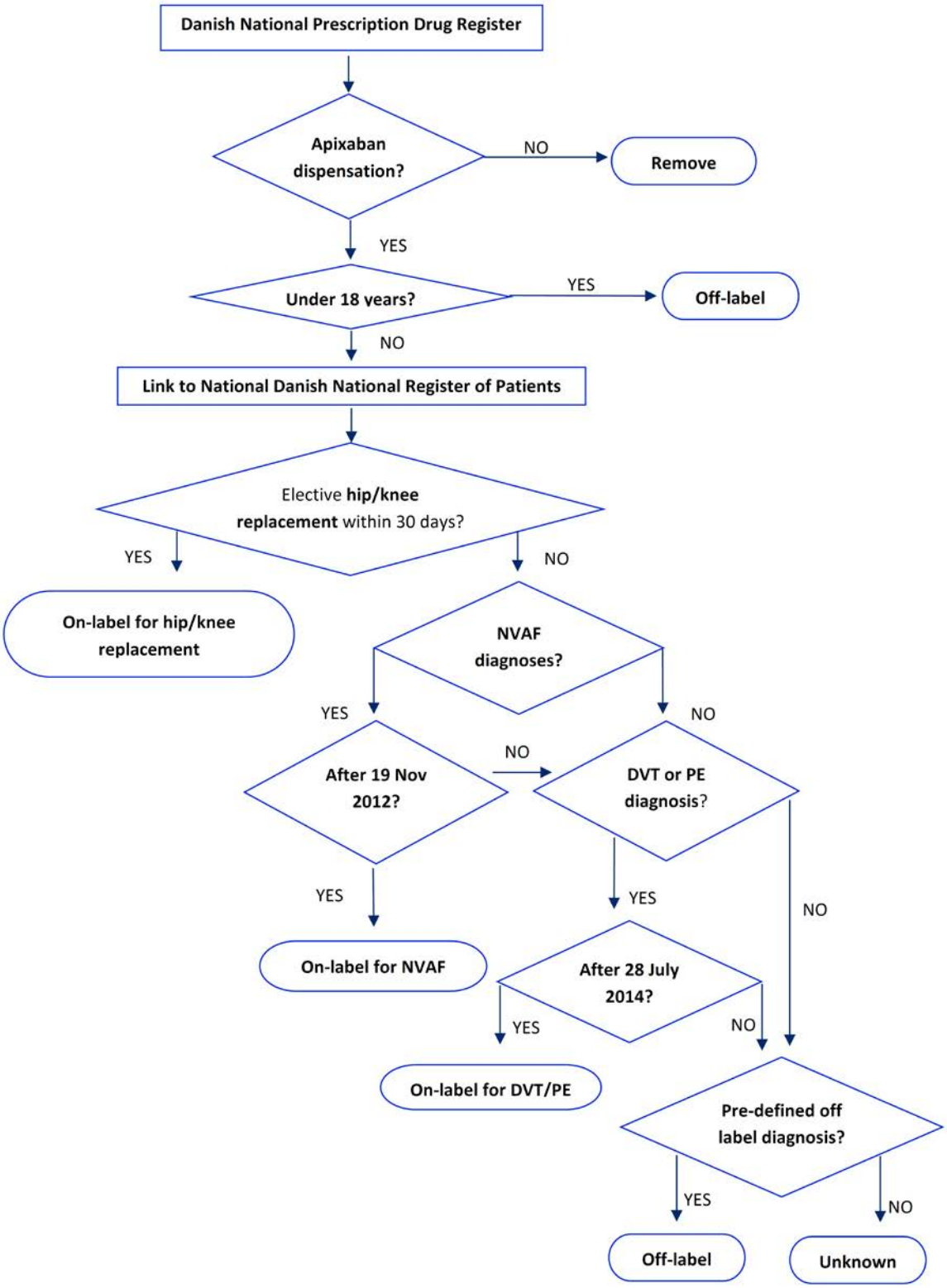
    - These may include but will not be limited to hip fracture surgeries, general surgeries, gynaecologic and abdominal surgeries, and diagnoses such as cancer, myocardial infarctions, other cardiac conditions, and other hypercoagulable states in which apixaban could be used off-label;

    - If multiple off-label indications are identified, patients will be classified by the off-label indication that is closest in time to the prescription, unless an apixaban patient has a mechanical heart valve. If a patient has a mechanical heart valve and any other potential off-label use then the mechanical heart valve will be reported;

- Investigators may add off-label uses during the analysis because not all the off-label uses can be identified prior to the study. The final report will indicate any additional off-label indications that were not described in the Statistical Analysis Plan (SAP).

6. Patients who have no evidence of the conditions for on-label use and who cannot be assigned to the list of pre-defined off-label uses will be classified as unknown (Figure 1).

Figure 1. Flow Chart for Data Linkage and On-Label or Off-Label Utilisation Classification



Variables relating to the prescriber, prescription, and patient will also characterise the pattern of apixaban usage (Table 2).

Table 2. Variable Data Sources and Definitions

Variable	Data source	Operational definitions
Age at apixaban dispensation	DCRS	Encoded in the personal identifier
Gender	DCRS	Encoded in the personal identifier
Concomitant medications and anticoagulant history	NHSPD	ATC codes for other anticoagulants and commonly prescribed medications
Morbidity	DNPR	ICD-10 code for renal disease, liver disorders, coagulation defects, and other morbidities found among apixaban users
Dispensation Date	NHSPD	Day, Month, Year
Dose	NHSPD	Daily Defined Dose
Quantity	NHSPD	Number of tablets
Duration of use	NHSPD	Inferred from quantity and date of dispensation and reported as number of days
Diagnoses for on-label and off-label indications	DNPR	ICD-10 codes for indications in Table 1 and described in the SmPC
Mechanical heart valves	DNPR	NOMESCO procedure codes and ICD-10 code
Date of diagnosis	DNPR	Day, Month, Year
Procedures and surgeries for on-label and off-label indications	DNPR	NOMESCO procedure codes for indications in Table 1 and described in the SmPC
Date of surgery	DNPR	Day, Month, Year
Date of hospital outpatient visit	DNPR	Day, Month, Year
Prescriber specialty	NHSPD	General practitioners and specialist types
On-label or off-label apixaban user classification	DNPR, NHSPD	Based on variables above including date of dispensation, diagnoses and procedures

ATC code: Anatomical Therapeutic Chemical code
DCRS: Danish Civil Registration System
DNPR: Danish National Patient Register
ICD-10: International Classification of Disease, Version 10
NHSPD: National Health Service Prescription Database
NOMESCO: Nordic Medico-Statistical Committee
SmPC: Summary of Product Characteristics

8.4. Data Sources

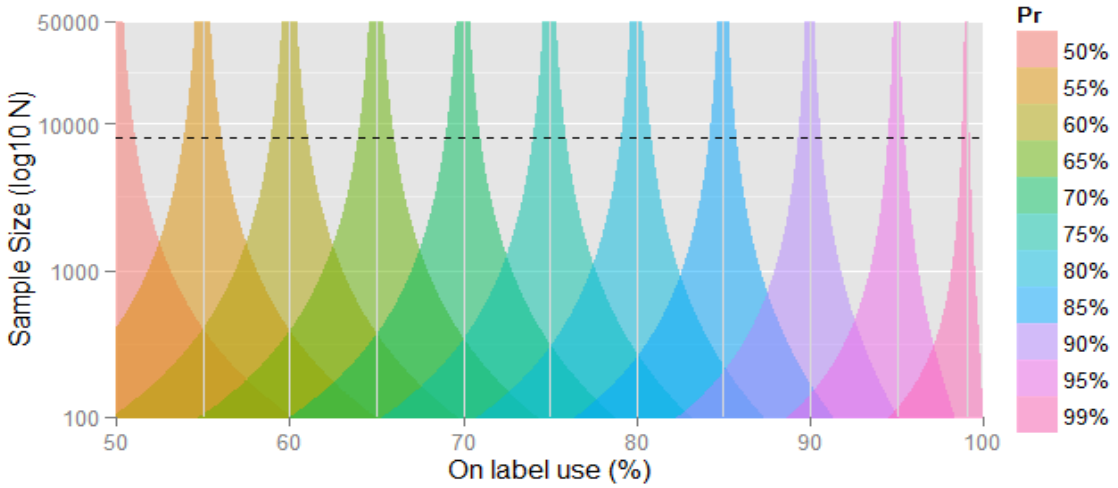
Denmark's health information systems are comprehensive, population-based, and contain prospectively collected data for the country's entire population of 5.6 million people. Databases, linked by a unique personal identifier, include the Danish Civil Registration System (DCRS), Danish National Patient Register (DNPR), and the Danish National Health Service Prescription Database (NHSPD). Inpatient and outpatient hospital data will be available through the DNPR, and outpatient prescription dispensations will be ascertained from the NHSPD.

8.5. Study Size

This descriptive study will not include any *a priori* hypotheses about the differences between patient groups so a formal sample size calculation to detect pre-defined effects is not applicable. However, a projected sample size of approximately 8000 patients dispensed with

apixaban from May 2011 through December 2014 is expected to provide sufficiently precise estimates of on-label and off-label use (Figure 2). At a sample size of 8000 patients, proportions that are separated by 5% (eg, 75%, 80%, 85%...) will be distinguishable with exact binomial confidence intervals. For instance, a proportion of on-label use of 75.0% (95% confidence interval [CI]: 74.0% - 75.9%), would differ sufficiently from an on-label proportion of 80.0% (95% CI: 79.1% - 80.9%).

Figure 2. Precision Around Proportions of On-Label Use



Precision around proportions (Pr) of on-label use. The widths of the vertical colored bars show exact binomial 95% confidence intervals for proportions of on-label use at sample sizes between 100 and 50,000 patients and proportions of on-label use between 50% and 99%. The dotted black horizontal lines represent a sample size 8000 patients.

8.6. Data Management

Data management and data analyses will be conducted using SAS Version 9.2 or higher according to the standard operating procedures at Aarhus University and Aarhus University's Department of Clinical Epidemiology.

8.7. Data Analysis

The data will be analysed and reported with proportions, medians, and other summary statistics. The distribution of patients receiving apixaban will be shown as the proportions of those using the medication for on-label, off-label, and unknown indications. Annual and cumulative proportions of use will be presented, as well as median times between the apixaban prescriptions and on-label or off-label diagnoses.

Additionally, the demographic and clinical characteristics of patients at the time of the apixaban prescription will be described. Morbidities (eg, renal or hepatic injury) and clinical procedures (eg, cardiac or oncological surgeries) prior to the prescription will be tabulated by on-label, off-label, and unknown patient classifications. Patients with a history of using warfarin or another NOAC will be shown to explore drug switching.

Specifically, the descriptive analysis will be performed in each of the indication strata to summarise:

1. Number of apixaban dispensations and dosing patterns.

2. Patients' demographics including age and gender.

3. Patients' morbidities, medical history and surgeries, including cardiovascular disease, renal impairment severe hepatic impairment, etc.

4. Patients' concomitant medication use, including contra-indicated medications.

5. Patients' history of treatment with other anticoagulants.

6. Prescribers' specialty.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the MAH. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality Control

Aarhus University and Aarhus University's Department of Clinical Epidemiology standard procedures will be followed to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, description of available data, and extent of validation of endpoints. All registry-based research in will be conducted in accordance with the Danish Act on Handling of Personal Data (www.datatilsynet.dk).

8.9. Limitations of the Research Methods

- The classification of on-label and off-label use of apixaban will be based on diagnoses from nationwide hospital discharge records and hospital outpatient clinics. However, diagnoses in the primary care setting will not be available. Missing primary care data may be particularly relevant for the NVAF indication because it is treated by primary care physicians, while TKR/THR surgery and DVT/PE treatment occur in the hospital. Systematic missing information of on-label NVAF users could lead to misclassification and bias. The patients with missing NVAF diagnosis data could be misclassified as off-label or unknown and result in an underestimate of on-label use.

- Only apixaban dispensed in the outpatient setting will be available. Therefore, patients who receive apixaban during a hospital stay and do not refill following discharge cannot be captured in this study.

8.10. Other Aspects

Not applicable

8.11. Strengths of the Research Method

- The study will use an established network of linkable databases that routinely collect information on the variables required to fulfill the objectives. There are strong linkage systems that utilize the unique national identifier of the patients to link different data sources. These registries have been used for many pharmacoepidemiologic studies,[9] including those looking at atrial fibrillation[10] and orthopedic surgery populations.[11]

- The registries have coverage of all age groups and all hospital admissions and discharge diagnoses in Denmark; they are representative of the Danish population.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any MAH forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the MAH will maintain high standards of confidentiality and protection of patient personal data.

9.2. Patient Withdrawal

Not applicable. The retrospective nature of these data makes patient withdrawal not applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

An application to conduct the study will be filed with the Danish Data Protection Agency (DPA) according to standard procedures. The study will commence after the DPA's permission is granted. All correspondence with the DPA will be retained in the Investigator File and copies of DPA approvals will be forwarded to MAH.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International

Organizations of Medical Sciences (CIOMS), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, Food and Drug Administration (FDA) Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event (AE) reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Investigators plan to submit the results of this study for publication. The study report will be posted on the EU PAS register.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this non interventional study protocol that the investigator becomes aware of.

12. REFERENCES

1. Mohanty BD, Looser PM, Gokanapudy LR, et al. Controversies regarding the new oral anticoagulants for stroke prevention in patients with atrial fibrillation. Vascular Medicine (United Kingdom). June 2014;19(3):190-204.

2. Hanna MS, Mohan P, Knabb R, Gupta E, Frost C, Lawrence JH. Development of apixaban: a novel anticoagulant for prevention of stroke in patients with atrial fibrillation. Annals of the New York Academy of Sciences. Nov 2014;1329:93-106.

3. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. Aug 31 2015.

4. Sorensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open 2013; 3(5):9 pages.

5. Molinier A, Acket B, Bourrel R, Lavezzi O, Montastruc JL, Bagheri H. Extrapolation of physiopathological data to clinical practice: Example of thrombosis-induced by off-label use of dabigatran. Fundamental and Clinical Pharmacology. May 2014;28:104.

6. Larock A-S, Mullier F, Douxfils J, Dogne J-M, Chatelain C, Spinewine A. Appropriateness Of Prescribing Of Direct Oral Anticoagulants: A Prospective Cohort Study At CHU UCL Mont-Godinne-Dinant. Blood. Vol 122:4809.

7. Carley B, Griesbach S, Larson T, Krueger K. Assessment of dabigatran utilization and prescribing patterns for atrial fibrillation in a physician group practice setting. The American journal of cardiology. Feb 15 2014;113(4):650-654.

8. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circulation. Cardiovascular quality and outcomes. 2012;5(5):615-621.

9. Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, Norgaard M, Almarsdottir A, Andersen M, Andersson Sundell K, Bergman U, Helin-Salmivaara A, Hoffmann M, Kieler H, Martikainen J, Mortensen M, Petzold M, Wallach-Kildemoes H, Wallin C, Sorensen H. The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. Pharmacoepidemiol Drug Saf 2013;22(7):691-9.

10. Friberg J, Gislason GH, Gadsboll N, et al. Temporal trends in the prescription of vitamin K antagonists in patients with atrial fibrillation. Journal of internal medicine. 2006;259(2):173-178.

11. Pedersen AB, Mehnert F, Johnsen SP, Sorensen HT. Risk of revision of a total hip replacement in patients with diabetes mellitus: a population-based follow up study. The Journal of bone and joint surgery. British volume. 2010;92(7):929-934.

Appendix 1. List of Stand Alone Documents

None.

Appendix 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post-Authorisation Safety Study (PASS) of the Utilisation Patterns of Apixaban in Denmark

Study reference number:
B0661073

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☐	☐	☒	NA
1.1.4 Interim progress report(s)	☐	☐	☒	NA
1.1.5 Registration in the EU PAS register	☒	☐	☐	7
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

There are no interim reports or progress reports for this study. It is expected to be completed in 1 year.

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7-8
2.1.2 The objective(s) of the study?	☒	☐	☐	8-9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	13

Comments:

This is a descriptive study with no a priori hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9-12
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	NA

Comments:

The study has primary objectives but no secondary objectives. As a descriptive, cross-sectional study, effect measures are not reported. Results are presented as total numbers, proportions and other summary statistics.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9
4.2.2 Age and sex?	☒	☐	☐	9
4.2.3 Country of origin?	☒	☐	☐	9
4.2.4 Disease/indication?	☒	☐	☐	9
4.2.5 Co-morbidity?	☒	☐	☐	9
4.2.6 Seasonality?	☒	☐	☐	9
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

The study describes apixaban use from 18 May 2011 through 31 Dec 2014 in Denmark (population 5.6 million). Any patient receiving apixaban in Denmark using routine outpatient dispensation records will be evaluated; there are no exclusion criteria for this study. Patients will be included regardless of age, sex, indication, co-morbidity, or seasonality.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	NA
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	NA
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	NA
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	NA

Comments:

As cross-sectional study that describes apixaban use patterns, there is not an exposure and outcome association examined. Apixaban use corresponds more closely with the outcome than the exposure.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	9-12
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	14

Comments:

The study does not include an endpoint that has a hypothesised association to a measured exposure. However, the proportion of on-label users and other descriptive statistics will address the objectives of the study.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	NA
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	NA

Comments:

Confounders and effect modifiers do not apply to this descriptive analysis.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	NA
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9-13
8.1.3 Covariates?	☐	☐	☒	NA

ENCePP Checklist for Study Protocols (Revision 2) 3

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	NA
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9-13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	NA
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	9-12
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9-12
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	NA
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	13

Comments:
Exposures and covariates do not apply to this descriptive analysis.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	13

Comments:
Precision around estimates of on-label use are discussed.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	NA
10.2 Is the choice of statistical techniques described?	☒	☐	☐	13
10.3 Are descriptive analyses included?	☒	☐	☐	14
10.4 Are stratified analyses included?	☒	☐	☐	14
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	NA
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	NA

Comments:
Excess risk, confounding and effect modification do not apply to this descriptive analysis.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	14
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	14
11.3 Are methods of quality assurance described?	☒	☐	☐	14

ENCePP Checklist for Study Protocols (Revision 2) 4

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	14-15
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	NA

Comments:

Patients with missing data will be classified as unknown. There is no independent review of these registry based, electronic data.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	NA
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	14-15
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13
12.3 Does the protocol address other limitations?	☒	☐	☐	14-15

Comments:

Selection bias is not discussed because all apixaban users in the Danish National Health system will be assessed.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	15-16
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	NA
13.3 Have data protection requirements been described?	☒	☐	☐	14

Comments:

The application to the Danish Data Protection Agency has not been made yet.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	16
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	16

Comments:

ENCePP Checklist for Study Protocols (Revision 2) 5

Name of the main author of the protocol: [redacted]

Date: 13/Nov/2015

[redacted]

Appendix 3. Additional Information

Not applicable.