Boehringer Ingelheim

Non-interventional Study Protocol

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BI Study Number:	1160-0287
BI Investigational Product(s):	Dabigatran etexilate (Pradaxa®)
Title:	Non-Interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-CONOCE Study.
Brief lay title	This study observes the use of new oral anticoagulants (NOACs) in patients with a heart rhythm disorder in Spain.
Protocol version identifier:	1.0
Date of last version of protocol:	24 July 2017
PASS:	No
EU PAS register number:	Study will be registered in EU PAS register
Active substance:	B01AE07 - Dabigatran etexilate
Medicinal product:	Dabigatran etexilate
Product reference:	EU/1/08/442
Procedure number:	EMEA/H/C/829
Marketing authorisation holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein This study is initiated, managed and sponsored by:
Joint PASS:	No
Research question and objectives:	**Primary objective**: The primary objective of the study is to describe the usage of NOACs in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation.

	Secondary objectives: - To evaluate the appropriateness of prescribed therapy based on Spanish health authorities' recommendations (positioning therapeutic report) - To describe NOAC treatment management. - To describe the patient's knowledge about anticoagulant treatment, independent of NOAC type.
Country of study:	Spain
Author:	(Trial Clinical Monitor) Mobile:
Marketing authorisation holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein This study is initiated, managed and sponsored by:
Date:	24 Jul 2017

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
AF	Atrial Fibrillation
ALT	ALanine Transaminase
AST	ASpartate Transaminase
BP	Blood Pressure
CA	Competent Authority
CHA_2DS_2-VASc score	Congestive heart failure, Hypertension, Age (> 75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex Category
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DMP	Data Management Plan
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol
ICH	IntraCraneal Hemorrhage
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
LPVM	Local PharmacoVigilance Manager
MAH	Marketing Authorization Holder
NIS	Non-Interventional Study
NVAF	Non Valvular Atrial Fibrillation
NOAC	New Oral Anticoagulant
PASS	Post-Authorization Safety Study
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics

TTR	Time in Therapeutic Range
VKA	Vitamin K Antagonists

3. RESPONSIBLE PARTIES

Medical Advisor	
Trial Clinical Monitor	
LPVM	
Coordinating Investigator	
Coordinating Investigator	
Coordinating Investigator	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Protocol date: 24 Jul 2017	**Study number:** 1160-0287	**Version/Revision:**	**Version/Revision date:**
Title of study:	Non-Interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-CONOCE study.		
Rationale and background:	Atrial fibrillation (AF) affects 1-2% of general population, but specially persons between 80 - 85 years, in whom the prevalence can reach 17% (1-3). In Spain, the latest data showed that prevalence of NVAF between general population is 4,4% in patients > 40 years-old and rises steeply above 60 years of age (3). One of the most concerning sequelae associated with AF is ischemic stroke with an incidence of about 5 % per year in the absence of appropriate prophylaxis (4). The current clinical guidelines for the management of atrial fibrillation recommend that patients with an embolic risk factor receive preventive anticoagulant therapy (5). The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocoumarol. The management of these agents remains problematic because they require frequent routine coagulation monitoring and dose adjustment to maintain the intensity of anticoagulation within a safe and effective range. However, data show that 80% of patients receiving acenocoumarol in Spain, maintain a percentage of International Normalized Ratio (INRs) in therapeutic range between 44% -59% (6,7) and mean time in therapeutic range (TTR) of only 64% (6). Another recent study has showed that 40% of patients with NVAF who were receiving anticoagulation therapy with VKA in primary care in Spain had poor anticoagulation control (8). The NOAC maintain the benefits of anticoagulant therapy and may increase perception of quality of life and satisfaction among patients because they do not necessitate the strict monitoring required for VKA. Likewise, maintaining a stable level of anticoagulation with NOACs prevents uncontrolled patients, improving patient outcomes and avoiding bleeding events (9). The importance of this proposed novel study lies in the new scenario in anticoagulation therapy in Spain which involves: - Recent publications in RWE which compares efficacy and		

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	safety among different NOACs (10). - Recent launch of Praxbind to market (June 2016). - Changes in anticoagulants' prescription Spanish National guidelines - positioning therapeutic report (November 2016). (11) - Launch of new alternative (Edoxaban) to market (September 2016). All this topics could influence the prescription habits and positioning the different NOACs in different patient's profile, according their clinical characteristics. Furthermore, patient could play a new role in this scenario, with a higher empowerment in decisions about his condition. Based on this assumption, it's considered interesting to describe the current the anticoagulation management in Spain.		
Research question and objectives:	This study has been designed in order to describe the current anticoagulation management in Spain. **Primary objective**: The primary objective of the study is to describe the usage of NOACs in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation. **Secondary objectives:** - To evaluate the appropriateness of prescribed therapy based on Spanish health authorities' recommendations (positioning therapeutic report) - To describe NOAC treatment management. - To describe the patient's knowledge about anticoagulant treatment, independent of NOAC type.		
Study design:	This is an observational, multicentre, cross-sectional study based on newly collected data that will be conducted in cardiology departments, in at least 102 centers in Spain.		

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Population:	Patients, in the hospital setting, will be included in the study if all of the following criteria are met: 1. The patient is willing and provides written informed consent to participate in this study 2. The patient is at least 18 years of age 3. The patient has a diagnosis of non-valvular atrial fibrillation (NVAF) 4. The patient is on treatment with NOAC according to its approved local SmPC and has initiated his first NOAC starting from November 2016 Patients will be excluded from participating in this study if they currently participate in any clinical trial of a drug or device. To minimize selection bias at the patient level, 10 consecutive patients from each site who meet entry criteria will be enrolled.		
Variables:	<u>Variables collected at time of first NOAC initiation (baseline data collected from medical records)</u>: - Demographic characteristics (age, gender, work status, life status) - Alcohol consumption - Physical activity - Systolic BP/Diastolic BP - CHA2DS2-VASc - HAS-BLED - AF diagnosis date - In case of previous treatment with VKA: treatment duration (start and stop date if available) and reasons for VKA treatment switch - First NOAC initiated (active substance, dose, start date) - Kidney function (serum creatinine (mg/dl), creatinine clearance (CG equation) obtained from medical charts or auto-calculated) - Liver function (AST/ALT, total bilirubin) - Other concomitant diseases (focused on those related with stroke and systemic embolism prevention in patients with NVAF) - Concomitant treatments (focused on those related with stroke and		

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	systemic embolism prevention in patients with NVAF) - To evaluate the reason of NOAC initiation. <u>Variables collected at time of study visit / enrolment (new data):</u> - In order to answer the secondary objective regarding patient's knowledge, all patients at study visit will be asked some questions by the physician. - In order to answer the secondary objective regarding treatment management, the following variables will be collected: - History of NOAC treatments prior to current NOAC (if applies): - Dose changes: start date – end date, new dose, reason - NOAC switch: start date – end date, dose and/or dose changes and reason - Frequency of visits to the physician - History of thromboembolic and bleeding events at time of enrolment Even though this NIS is based on already existing (retrospective) data and also new data obtained at the visit date, AE management and AE reporting becomes relevant as data extraction from patient's individual medical records will be performed (study data collection) and reviewed. AE management and reporting has to be implemented and followed as outlined in section 11.		
Data sources:	Patient data will be collected from patient medical charts and will be entered to an eCRF by the Investigator. Most of data will be available in the charts but as a routine clinical practice, some data could be missing. Data regarding the ad hoc questionnaire will be obtained from an interview between the physician and the patient according to instructions. Investigator will enter these data into the eCRF system.		
Study size:	It is planned that a total of approximately 1000 patients will be recruited for the study. Additional details regarding sample size considerations are provided in Section 9.5.		
Data analysis:	A Data Management Plan (DMP) and Statistical and Epidemiological Analysis Plan (SEAP), will be prepared to describe all processes, treatment and specifications for data collection, cleaning, validation		

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	and analysis. Since the study is descriptive, the variables included in the study objectives will be summarized overall and by factors of interest. All results will be summarized with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges. The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria). If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. Missing data will not be imputed.		
Milestones:	- Final Protocol: Jul 2017 - Start of data collection: November 2017 - End of data collection: May 2018 - Final study report: October 2018		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Sep 2017
Start of data collection	Nov 2017
End of data collection	May 2018
Registration in the EU PAS register	Jul 2017
Final report of study results:	Oct 2018

7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) affects 1-2% of general population, but specially persons between 80 - 85 years, in whom the prevalence can reach 17% [1-3]. In Spain, the latest data showed that prevalence of NVAF in general population is 4.4% in patients > 40 years-old and rises steeply above 60 years of age [3].

One of the most concerning sequelae associated with AF is ischemic stroke with an incidence of about 5 % per year in the absence of appropriate prophylaxis [4]. The current clinical guidelines for the management of atrial fibrillation recommend that patients with an embolic risk factor receive preventive anticoagulant therapy [5].

The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocoumarol. The management of these agents remains problematic because they require frequent routine coagulation monitoring and dose adjustment to maintain the intensity of anticoagulation within a safe and effective range. However, data show that between 43,8 % to 59 % of the population receiving acenocumarol in Spain are within the recommended INR target of 2.0 – 3.0. [6]. Another recent study has showed that 40% of patients with NVAF who were receiving anticoagulation therapy with VKA in primary care in Spain had poor anticoagulation control [8].

The New Oral AntiCoagulants (NOACs) maintain the overall benefit of anticoagulant therapy and may increase perception of quality of life and satisfaction among patients because they not necessitate the strict monitoring required for VKA. Likewise, maintaining a stable level of anticoagulation with NOACs prevents uncontrolled patients, improving patient outcomes and avoiding bleeding events [9].

The importance of this proposed novel study lies in the new scenario in anticoagulation therapy in Spain which involves:

- Recent publications in RWE which compares efficacy and safety among different NOACs [10]
- Recent launch of Praxbind® to market (June 2016)
- Changes in anticoagulants' prescription Spanish National guidelines - positioning therapeutic report (November 2016) [11]
- Launch of new alternative (Edoxaban) to market (September 2016).

All these topics could influence the prescription habits and positioning the different NOACs in different patient's profile, according their clinical characteristics. Furthermore, patients could play a new role in this scenario, with a higher empowerment in decisions about their condition. Based on this assumption, it's considered interesting to describe the current anticoagulation management in Spain.

8. RESEARCH QUESTION AND OBJECTIVES

This study has been designed in order to describe the current anticoagulation management in Spain.

Primary objective:
To describe the usage of NOACs in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation. Baseline clinical and demographic characteristics of patients will be described according to NOAC used.

Secondary objectives:

- To evaluate the appropriateness of prescribed therapy based on Spanish health authorities recommendations (positioning therapeutic report)
- To describe NOAC treatment management.
- To describe the patients' knowledge about anticoagulant treatment, independent of NOAC type.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This observational multi-centre and cross-sectional study will be conducted in cardiology departments, in at least 102 centres in Spain.

The design of the study impose an only visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

A specific therapeutic strategy has already been assigned to each included patient, based on routine practice and without interference with the physician's prescription habits. The observational nature of the study is ensured as no diagnostic or therapeutic intervention outside of routine clinical practice will be applied.

Figure 1 Study design

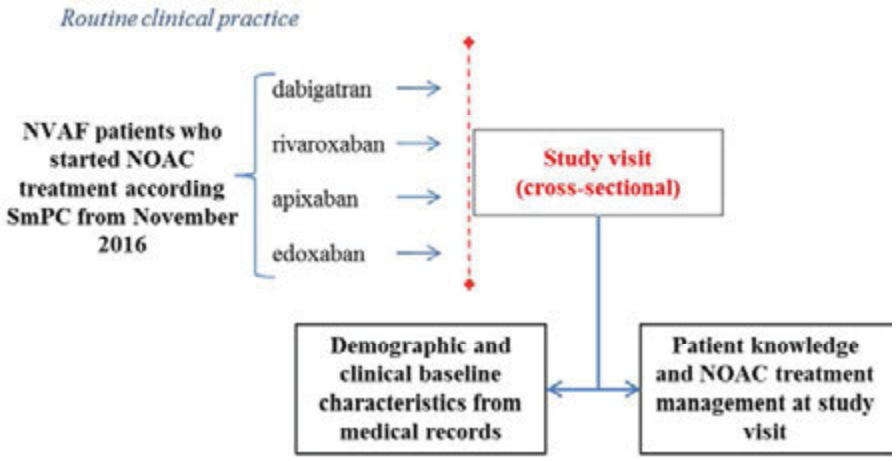

Figure 1 has been designed according to Spanish Health Authorities recommendations, which recommend start OAC treatment with VKA. However in some circumstances, NOAC could be considered as primary treatment choice according to the positioning therapeutic report:

1. Clinical reasons:
   - Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin.
   - Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase)
   - Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH.
   - Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control.
2. Situations related to INR control:
   - Patients who have started treatment with VKA in which it is not possible to maintain INR control within range (2-3) despite good therapeutic compliance.

- Impossibility of access to conventional INR control.

9.2 SETTING

Approximately 1.000 patients with NVAF currently on NOAC treatment and having initiated their first NOAC starting from November 2016 (Health Authorities positioning report publication) are planned to be included in the study. To minimize selection bias at the patient level, 10 consecutive patients from each site who meet entry criteria will be enrolled.

It is necessary to ensure that study population is representative of the entire national territory. Therefore, patients will be recruited from Hospitals (different levels of medical care: primary hospital, secondary hospital) in different geographical areas according to the distribution of the overall population in this area. Site selection will be performed in order to secure representativeness of the NVAF population treated with NOACs.

9.2.1 Study sites

Cardiology departments, in a hospital setting, who regularly prescribe NOACs for stroke prevention in NVAF patients, will be selected to participate. The study will be performed among all the national territory. Site feasibility assessments will be performed by the CRO during the process of site selection.

9.2.2 Study population

To be eligible to participate in the study, patients must meet the following selection criteria. The patient will be considered included when he/she agrees to participate in the study by signing the informed consent.

Patients will be <u>included</u> in the study if all of the following criteria are met:

1. The patient is willing and provides written informed consent to participate in this study
2. The patient is at least 18 years of age
3. The patient has a diagnosis of non-valvular atrial fibrillation (NVAF)
4. The patient is on treatment with NOAC according to its approved local SmPC and has initiated his first NOAC starting from November 2016

Patients will be <u>excluded</u> from participating in this study if they currently participate in any clinical trial of a drug or device.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the study file at the study site.

9.2.3 Study visits

The design of the study imposes a single visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator. After signing the informed consent

(if patient agreed to participate in the study) patients will be asked to answer the questions necessary to evaluate the patient's knowledge about anticoagulant treatment at the unique study visit. Other variables needed to address study objectives will be obtained directly from patient medical records. The end of the single study visit is the end of the study for each patient.

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study
3. Violation of the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

Patients in this study will have been prescribed a NOAC treatment for their NVAF and initiated it in the time period from November 2016 to present. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before the study visit. The study population will be treated with NOAC according to the approved local Summary of Product Characteristics (SmPC).

As this is a non-interventional observational study, designed to reflect as faithfully as possible real-life clinical practice, the decision to start treatment with NOAC is prior to and independent of the participation of the patient in the study and based on medical judgment criteria and routine clinical practice. In addition, no intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome is the usage of NOACs, in patients with NVAF, in the hospital setting, based on the baseline characteristics at the time of first NOAC initiation. Baseline (at time of first NOAC initiation) variables will be analysed descriptively by NOAC type. Treatment groups will be defined according to first NOAC prescribed. The time frame for assessing this outcome is 7 months (recruitment period).

Table 9.3.2.1: 1 Baseline variables at time of first NOAC initiation

Variables	Obtained from patient medical records
Age	X
CHA_2DS_2-VASc	X
HAS-BLED	X

9.3.2.2 Secondary outcomes

The secondary outcomes are:

- Appropriateness of NOAC prescription based on national recommendations (positioning therapeutic report) (11) is planned. The reasons for NOAC initiation will be described using the following checklist. The time frame is the duration of the study visit, at the time of patient enrolment. Answers to this checklist will be validated with baseline variables already collected from medical records:

    - □ Patients with known hypersensitivity or with specific contraindications to the use of acenocoumarol or warfarin.
    - □ Patients with a history of intracranial hemorrhage (ICH) (except during the acute phase)
    - □ Patients with ischemic stroke who present high-risk clinical and neuroimaging criteria for ICH.
    - □ Patients on VKA treatment who suffer from severe arterial thromboembolic events despite good INR control.
    - □ Patients who have started treatment with VKA in which it is not possible to maintain INR control within range (2-3) despite good therapeutic compliance.
    - □ Impossibility of access to conventional INR control.
    - □ Other
    - □ Unknown

- NOAC treatment management. The following variables will be collected at time of patient enrolment:
    - history of thromboembolic and bleeding events,
    - frequency of visits to the physician,
    - first NOAC (start - end date, dose),
    - dose change/adjustment (start date - end date, new dose, reason for change)
    - new NOAC initiation (start - end date, new treatment, new dose, reason for change)

  Prior VKA use and reasons for switch (already collected as a baseline variable) will be also considered for this outcome. The time frame is the duration of the NOAC treatment, since first NOAC treatment initiation until the study visit date.

- Patient's knowledge about his condition. Answers (yes/no) to the questions below will be described for the whole study population, independent of NOAC type. "Yes" and "No" patient's answers must be validated by the physician (the physician will ensure that the answer is accurate by asking "Why" "Which" "What" additional questions to validate the answer). The time frame is the duration of the interview with the patient during the study visit, at the time of patient enrolment.

    a) Do you know why you are being treated with an anticoagulant? Yes/No.
    b) Do you know which the effect of the anticoagulant treatment is? Yes/No.
    c) Do you know what could happen if you don't take the anticoagulant treatment? Yes/No.
    d) Do you mind taking the anticoagulant treatment? Yes/No.

Table 9.3.2.2:1 Treatment management variables at time of enrolment

Variables	Obtained from patient medical records	Obtained at the study visit by direct interview with the patient
In case of previous treatment with VKA: treatment duration (start and stop date if available) and reasons for VKA treatment switch	X *	
First NOAC initiated (active substance, dose, start date, end date)	X *	
History of thromboembolic and bleeding events	X	X (if applicable)
History of NOAC treatments prior to current NOAC (if applies): - Dose changes: start date – end date, new dose, and reason - NOAC switch: start date – end date, dose and/or dose changes and reason	X	X (if applicable)
Frequency of visits to the physician: "How many times a year do you visit the cardiologist?"		X

* Already obtained for primary objective.

9.3.3 Covariates

Table 9.3.3: 1 Covariates: Baseline variables at time of first NOAC initiation

Variables	Obtained from patient medical records
Demographic characteristics (gender, work status, life status)	X
Alcohol consumption	X
Physical activity	X
Systolic BP/Diastolic BP	X
AF diagnosis date	X
In case of previous treatment with VKA: treatment duration (start and stop date if available) and reasons for VKA treatment switch	X
First NOAC initiated (active substance, dose, start date, end date)	X
Kidney function (serum creatinine (mg/dl), creatinine clearance (CG equation) obtained from medical charts or auto-calculated)	X
Liver function (AST/ALT, total bilirubin)	X
Concomitant and relevant previous diseases (Ischaemic stroke or TIA, Systemic embolism, Heart Failure, Coronary artery disease, Ischemic cardiomyopathy, Left ventricular dysfunction, Cerebrovascular disease, Renal disease, Liver disease, Bleeding, Hypertension, Diabetes mellitus, Hyperlipidemia, COPD, Gastric and duodenal ulcers, Dementia, Anemia, Rheumatic disease, Cancer, Prosthetic heart valves, Others)	X
Concomitant treatments (ARB or ACE inhibitor, Beta-blocker, Calcium channel blockers, Diuretics, Amiodarone, Statin, Proton-pump inhibitor, H2-receptor antagonist, Aspirin, Other Antiplatelet agents, Digoxin, NSAIDs, Verapamil / Dronedarone, Other antiarrhythmics, ketoconazol (systemic), ciclosporine, itraconazol, Others)	X

9.4 DATA SOURCES

Data collection will be limited to those available in the medical records of selected patients.

Variables collected at time of first NOAC initiation (see Table 9.3.2.1: 1 and Table 9.3.3 :1) will be obtained based on patient's medical records.

Patient knowledge about his condition and other variables collected at time of patient enrolment (new data, see Table 9.3.2.2: 1) will be obtained by interviewing the patient.

9.5 STUDY SIZE

It is planned that a total of approximately 1000 patients will be recruited for the study.
Based on such sample size estimates, categorical variables of binomial proportions (e.g. gender) will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in the table 9.5: 1.

Table 9.5: 1 Width of 95% confidence interval by precision

Prevalence of attribute		Sample size 1000
10%	Expected n	100
	95% CI width	3.73
20%	Expected n	200
	95% CI width	4.95
30%	Expected n	300
	95% CI width	5.67
40%	Expected n	400
	95% CI width	6.06
50%	Expected n	500
	95% CI width	6.18

9.6 DATA MANAGEMENT

The data will be entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous.

AE reconciliation will be performed quarterly from study initiation date.

When data management is outsourced, the designated contract organization will be responsible for the development and implementation of the data management plan and preparation of the data handling report according to the sponsor´s standards.
The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

Analyses will be performed by Boehringer Ingelheim's designees. The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria). If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

In this non-interventional study, retrospective data from medical charts and data at the study visit will be collected for non-valvular AF patients. Once the study has been completed and all data from the last patient have been recorded, the database will be closed and statistical analysis will be performed.

The proposed methods for statistical analysis presented below are a summary of the methods that will be applied in the study to analyse the data collected and to answer the study objectives.

Since the study is descriptive the variables included in the study objectives will be summarized overall and by factors of interest. All results will be summarized with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges.

A Statistical and Epidemiological Analysis Plan (SEAP), will be prepared to describe all processes, treatment and specifications for and the planned statistical analysis.

9.7.1 Main analysis

The primary outcome is the usage of NOACs in patients with NVAF, based on the baseline characteristics at the time of first NOAC initiation. Baseline (at time of first NOAC initiation) variables will be analyzed descriptively by NOAC type. Standardized differences between Dabigatran Etexilate and each of the other NOACs separately will be estimated for these variables.

For the secondary outcomes, the following analyses are planned:

Appropriateness of NOACs prescription based on national recommendations (positioning therapeutic report) (11) is planned to be done for the entire eligible patients.

For NOAC treatment management, descriptive analysis of history of thromboembolic and bleeding events, frequency of visits to the physician, first NOAC (start - end date, dose), dose change/adjustment (start date - end date, new dose, reason for change) and new NOAC initiation (start - end date, new treatment, new dose, reason for change) will be done. Prior VKA use and reasons for switch (already collected as a baseline variable) will be also considered for this outcome.

Variables regarding patient knowledge collected at time of patient enrolment will be analysed descriptively (independent of NOAC type). Each question will be analyzed separately.

9.8 QUALITY CONTROL

The eCRF will include programmable edit checks to obtain feedback if data is missing, out of range, illogical or potentially erroneous. These checks will be performed once data is entered into the eCRF. Thus the data entered in to the eCRF will be validated within the system and the physician will receive alerts for missing or inconsistent data. In case any changes of already entered data will be required, an audit trail will be available.

No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit could be performed.

Strict and continuous quality control will be maintained to ensure the accuracy and scientific rigor of the data obtained, maintaining uniform conditions for collecting the information. Quality control will be carried out by qualified personnel designated for this purpose.
A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent document of this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

A NIS is the most suitable design to obtain information about the use of medicines in everyday therapeutic practice and thus for investigating questions in everyday therapeutic practice. However, there are some limitations inherent to this design.

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are less restrictive than the ones of a randomized clinical trial, which will permit the enrolment of a broader patient population.

The choice of NOAC was done before the study visit and it is done at the discretion of the investigator. However, as the setting is limited to the hospital setting (Cardiology Services), patients treated in other clinical settings will not be part of this study. Patients seen by their physician less than twice per year are therefore less likely to be included in the study. Patients with higher frequency of visits are more likely to be included in the study and could be over-represented in the sample. Additionally, having 10 patients recruited in each site, patients from the larger practice hospitals will also be under-represented.

As patients are included after first NOAC initiation and need to be treated by a NOAC at time of enrolment, any patient having prematurely discontinued any NOAC treatment between the time of first NOAC initiation and the start of the enrolment period will not be included in the study. The sample may therefore not be representative of all patients having initiated a NOAC since November 2016.

Channeling bias is a form of confounding that occurs when a drug is preferentially prescribed to patients with different baseline characteristics. Standardized differences will be applied when assessing channeling bias.

9.10 OTHER ASPECTS

Not applicable

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1

9.10.3 Completion of study

The EC/competent authority in Spain needs to be notified about the end of the study (last patient out), or early termination of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the competent authority.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring

and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:
No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

Once informed consent is signed the following must be collected by the investigator if identified during chart review data collection period and study visit data collection

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

All ADRs , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).

- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Pradaxa®, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **serious ADRs** associated with Pradaxa®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Pradaxa®	immediately within 24 hours
All **non-serious ADRs** associated with Pradaxa®	7 calendar days

All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than Pradaxa® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.
Final study report will be distributed to national health authority and ethics committees.
The results of this study will be published in a national journal and presented in regional or national congresses.

13. REFERENCES

13.1 PUBLISHED REFERENCES

[1] Barrios V, Calderon A, Escobar C, de la Figuera M. Patients with atrial fibrillation in a primary care setting: Val-FAAP study. Rev Esp Cardiol (Engl Ed) 2012 Jan;65(1):47-53.

[2] Cea-Calvo L, Redon J, Lozano JV, Fernandez-Perez C, Marti-Canales JC, Llisterri JL, et al. [Prevalence of atrial fibrillation in the Spanish population aged 60 years or more. The PREV-ICTUS study]. Rev Esp Cardiol 2007 Jun;60(6):616-24.

[3] Gomez-Doblas JJ, Muniz J, Martin JJ, Rodriguez-Roca G, Lobos JM, Awamleh P, et al. Prevalence of atrial fibrillation in Spain. OFRECE study results. Rev Esp Cardiol (Engl Ed) 2014 Apr;67(4):259-69

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[5] Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7;37(38):2893-2962.

[6] Ansell J, Hollowell J, Pengo V, Martinez-Brotons F, Caro J, Drouet L. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). J Thromb Thrombolysis 2007 Apr;23(2):83-91.

[7] Clua Espuny JL, Dalmau Llorca MR, Aguilar MC. [Characteristics of oral anti-coagulation treatment in high-risk chronic auricular fibrillation]. Aten Primaria 2004 Nov 15;34(8):414-9.

[8] Barrios V, Escobar C, Prieto L, et al. Anticoagulation Control in Patients With Nonvalvular Atrial Fibrillation Attended at Primary Care Centers in Spain: The PAULA Study. Rev Esp Cardiol (Engl Ed). 2015 Sep;68(9):769-76.

[9] Connolly SJ, Ezekowitz MD, Yusuf S et al. RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 17(361):1139–1151.

[10] Graham DJ, Reichman ME, Wernecke M et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. JAMA Intern Med. 2016 Nov 1;176(11):1662-1671

[11] General criteria and recommendations for the use of direct oral anticoagulants (NOAC) in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Spanish Health Authority Therapeutic Positioning Report. Version 5 (2016). Available at: https://aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm#anticoagulantes-orales.

[12] López-Sendon J, Merino JL. Mal control de la anticoagulación en la fibrilación auricular. Hasta cuándo? Rev Esp Cardiol. 2015;68(9):740–742.

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Title
<1>	Patient information and Informed Consent Form
<2>	Investigator List
<3>	Statistical Analysis Plan (SAP)
<4>	Data Management Plan (DMP)
<5>	Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
<6>	Pregnancy Monitoring Form

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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:
Non-Interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-CONOCE Study.

Study reference number:
1160-0287

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[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.

Comments:

Study progress reports for EC and authorities will be done annually

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

Comments:

No hypothesis testing is planned in this descriptive study in section 9.7

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Descriptive study. No measures of occurrence or measures of association are performed

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	10.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Cross-sectional study. No follow-up is carried out

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Observational study. Patients treated as per routine clinical practice.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Descriptive outcomes

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

This study is only descriptive

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

Comments:

This study is only descriptive

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.2

Comments:

Unique patient identification code numbers will be used.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

This study is only descriptive

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.2

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2

Comments:

This study is only descriptive

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

APPROVAL / SIGNATURE PAGE

Document Number: c18718851 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Non-Interventional, cross-sectional study to describe NOACs management in patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-CONOCE Study.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Medical		25 Jul 2017 10:43 CEST
Approval- Safety Evaluation Therapeutic Area		25 Jul 2017 12:07 CEST
Approval-Team Member Medical Affairs		27 Jul 2017 11:25 CEST
Approval-Biostatistics		27 Jul 2017 14:09 CEST
Approval-Therapeutic Area		30 Jul 2017 12:28 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed