STATISTICAL ANALYSIS PLAN

Version 3.0

29/11/2018

RESONANCE	OBSERVATIONAL STUDY DESCRIBING TREATMENT CONVENIENCE IN PATIENTS TREATED WITH DABIGATRAN FOR STROKE PROPHYLAXIS IN NON-VALVULAR ATRIAL FIBRILLATION

Sponsor

Boehringer Ingelheim

PAGE OF SIGNATURES

	Responsible	Signature	Date (dd/mmm/yyyy)
Prepared by:	Statistician		
Reviewed by:	Project		
Approved by:	Boehringer Ingelheim		
	Boehringer Ingelheim		

1. GENERAL INFORMATION ABOUT THE STUDY

1.1. SPONSOR IDENTIFICATION

Boehringer Ingelheim España, S.A.

Prat de la Riba, 50

08174 Sant Cugat del Vallès

Barcelona, Spain

1.2. STUDY TITLE

Observational Study Describing Treatment Convenience in Patients Treated With Dabigatran for Stroke Prophylaxis in Non-Valvular Atrial Fibrillation.

1.3. PROTOCOL CODE

BI 1160.253

1.4. COORDINATING INVESTIGATORS

1.5. TYPE OF SITES WHERE THE STUDY IS BEING CONDUCTED

The study is being conducted at approximately 200 cardiology centres and non-specialist centres where Pradaxa® and VKAs are regularly prescribed for stroke prophylaxis in NVAF,

under regular medical practice conditions and in accordance with daily clinical practice. These centres are located in four Autonomous Communities.

1.6. CENTRAL IEC EVALUATING THE STUDY

Hospital Universitario La Paz IEC

Paseo de la Castellana, 261

Planta 8ª Hospital General

28046 Madrid

1.7. PRIMARY OBJECTIVE

The primary objective of this study is to describe patients' perception of their treatment for NVAF using the PACT-Q2 questionnaire at three time points: during the baseline period (after the indication for Pradaxa®), after approximately one month and during the continuation period.

1.8. STUDY DESIGN

National, multi-centre, observational study based only on obtaining new data. The study will enrol patients in Spain with NVAF who are treated with VKAs and subsequently start Pradaxa®, and who have given their consent.

Patients will be monitored for a period of six months. Data will be collected at three time points:

1. After the indication for Pradaxa® (baseline period)

2. 30-45 days after starting treatment with Pradaxa® (initial period)

3. 150-210 days after starting treatment with Pradaxa® (continuation period)

The visit windows above for Visit 2 and Visit 3 should be seen as guidance for the treating physician. Visit schedule deviations are expected as the visits are being scheduled according to local clinical routine. For analysis purpose, Visit 2 data that were collected between 7 and 124 days after initiation will be included (rationale for the lower limit is that steady state on Pradaxa® is achieved after 3 days, and first side effects also might occur after a 1st or 2nd intake; rationale for the higher limit is to make sure that there is no overlap with Visit 3). Visit

3 data that were collected between 125 and 365 days after initiation will be included for analysis.

Due to Pradaxa® initiation date was not recorded in the eCRF, it is assumed that the initiation date of Pradaxa® is the day after the VKA end date.

1.9. DISEASE OR DISORDER UNDER STUDY

Non-valvular atrial fibrillation with a risk of stroke.

1.10. INFORMATION ON THE STUDY MEDICATION

- Pradaxa ® 110 mg hard capsules
- Pradaxa ® 150 mg hard capsules

Pradaxa® 110 mg and Pradaxa® 150 mg hard capsules contain dabigatran etexilate (active substance: dabigatran).

Patients will receive a single daily dose of Pradaxa® in accordance with the product's Summary of Product Characteristics, the Therapeutic Positioning Report issued by the competent authorities in Spain and the authorisations of the various autonomous communities.

The current version of the Summary of Product Characteristics (SmPC) for Pradaxa® can be found on the EMA's website.

The following link is updated with the most recent authorised version of the SmPC:

http://ec.europa.eu/health/documents/community-register/html/h442.htm

1.11. STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

The study population is made up of patients with a diagnosis of NVAF who are suitable for transfer from treatment with VKAs to treatment with Pradaxa®, in accordance with the Summary of Product Characteristics for Pradaxa®. Patients will be enrolled in the study following the decision to start treatment with Pradaxa®. The decision to start treatment with Pradaxa® is based on the recommendations of the health authorities described in the therapeutic positioning report for NOACs.

The planned enrolment is a total of 1087 patients from cardiology centres and non-specialist centres that regularly prescribe Pradaxa® and VKAs for stroke prophylaxis in NVAF in accordance with the recommendations of the health authorities described in the therapeutic positioning report for NOACs.

1.12. STUDY SCHEDULE

The estimated key dates are:

- Start of data collection: June 2016
- End of data collection: July 2018
- Final study report: January 2019

1.13. SOURCE OF FUNDING

The sponsor, Boehringer Ingelheim España, S.A., will pay for all expenses that may arise from the study, including: logistics management, statistical analysis and investigators' fees. The sponsor issues a financial report for the study, which details the fees that will cover the costs of participation for the site and the investigators.

Because the study is being conducted under the normal conditions of clinical practice, and because the patients will not undergo any diagnostic or follow-up procedure that is not a part of routine clinical practice, the study does not involve extraordinary expenses for the investigator or site other than the investigator's commitment to complete the required information on the electronic case report form designed for this purpose.

1.14. INFORMATION ON THE COORDINATING SITE

Tel.:

Fax:

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2. GLOSSARY OF ABBREVIATIONS

The meanings of the abbreviations used in this document are explained below:

AE:	Adverse Event
SAE	Serious Adverse Event
DOAC	Direct oral anticoagulant
AST/ALT	Aspartate aminotransferase/Alanine aminotransferase
VKA	Vitamin K antagonist
B	Beta
DB	Database
AC	Autonomous Community
IEC	Independent Ethics Committee
CRF	Case Report Form
eCRF	Electronic case report form
SD	Standard deviation
ECG	Electrocardiogram
EMA	European Medicines Agency
NVAF	Non-valvular atrial fibrillation
HR	Heart rate
ICH	Intracranial haemorrhage
CI	Confidence interval
BMI	Body mass index
INR	International Normalised Ratio
MedDRA	*Medical Dictionary for Regulatory Activities*
Min	Minimum
Max	Maximum
n	Number of cases

p	p-value associated with the statistical test used
DBP	Diastolic Blood Pressure
SAP	Statistical analysis plan
SBP	Systolic Blood Pressure
DMP	Data management plan
AR	Adverse reaction
SAS	*Statistical Analysis System*
ACS	Acute Coronary Syndrome
ACS-STEMI	Acute Coronary Syndrome. ST-segment elevation myocardial infarction
ACS-NSTEMI	Acute Coronary Syndrome. Non-ST-segment elevation myocardial infarction
SmPC	Summary of Product Characteristics
CNS	Central Nervous System

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to describe patients' perception of their treatment for NVAF using the PACT-Q2 questionnaire at three time points: during the baseline period after the indication for Pradaxa®, after approximately one month and during the continuation period:

- Visit 1 or baseline visit: when the patient is receiving treatment with VKAs for the prophylaxis of stroke/embolism and has changed treatment (baseline period to record the perception of treatment with VKAs). Patients will be enrolled in the study following the decision to start treatment with Pradaxa®. The decision to start treatment with Pradaxa® is based on the recommendations of the health authorities described in the therapeutic positioning report for NOACs.

- Visit 2 or initial period: when treatment with Pradaxa® has commenced (30-45 days).

- Visit 3 or continuation period: when continuing treatment with Pradaxa® (~180 days).

As indicated in section 1.8, Visit 2 data that were collected between 7 and 124 days after baseline will be included for analysis; Visit 3 data that were collected between 125 and 365 days after baseline will be included for analysis.

3.2. SECONDARY OBJECTIVES

Characterisation of the patient population in Spain:

- Demographic data (age, sex, comorbidities and concomitant medication)
- Obtaining elements assessed by the physician to calculate the HAS-BLED score during the baseline period.
- Obtaining elements assessed by the physician to calculate the CHA_2DS_2-VASc score during the baseline period.
- If available: analytical evaluation of kidney function and calculation of creatinine clearance using the Cockcroft-Gault formula.
- Initial Pradaxa® dose
- Reasons for changing the dose of Pradaxa® or discontinuing Pradaxa®/VKAs.

4. STUDY POPULATION

4.1. SELECTION CRITERIA

Patients who meet all the inclusion criteria and none of the exclusion criteria indicated below are considered eligible to take part in the study.

4.1.1. Inclusion criteria

1. Granting informed consent in writing prior to enrolment
2. Patients of both sexes ≥ 18 years of age with a diagnosis of NVAF.
3. Patients treated continuously with VKAs for stroke prophylaxis for at least six months prior to the baseline visit.
4. Patients switching to treatment with Pradaxa® in accordance with the recommendations of the competent health authorities described in the therapeutic positioning report for NOACs and the authorisations of the various autonomous communities.

4.1.2. Exclusion criteria

1. Contraindications for the use of Pradaxa® or VKAs described in the Summary of Product Characteristics (SmPC).
2. Patients receiving Pradaxa® or VKAs for any reason other than stroke prophylaxis in NVAF.
3. Participation in any clinical trial of an investigational medicinal product or medical device.

4.2. JUSTIFICATION FOR SAMPLE SIZE

The prospective collection is planned of data from approximately 1087 patients by approximately 200 principal investigators at cardiology and internal medicine centres and non-specialist centres that regularly prescribe dabigatran and VKAs for stroke prophylaxis in NVAF in accordance with the recommendations of the health authorities described in the therapeutic positioning report for direct oral anticoagulants (DOACs).

The participating centres are located in the autonomous communities of Catalonia, Galicia, Andalusia and the Basque Country.

As is established in the study protocol, due to the limited number of publications on the PACT-Q questionnaire (see reference studies in the Bibliography section of the protocol) and the absence of information on the clinical significance of variations in the PACT-Q scale, the sample size has been calculated using standardised mean differences. Specifically, in the context of this study, these represent the mean differences in the PACT-Q questionnaire score obtained at two different time points, divided by the corresponding standard deviations. Generally, a standardised effect size of 0.2 is considered to represent a small change, 0.5 represents a moderate change and 0.8 a large change.

Assuming a two-sided alpha level of 0.05 and a 20% loss to follow-up, a sample size of 1087 patients will give a statistical power of 90% for the detection of a standardised mean difference of 0.11 for the primary endpoint, the evaluation of PACT-Q2 questionnaire scores obtained during the final and baseline assessments.

5. METHODS

5.1. DATA PROCESSING

The data will be collected by each investigator through an electronic case report form (eCRF). All the data from the eCRFs will be entered into a database created for this purpose and set up with ranges and rules for internal consistency, to ensure quality control of the data.

5.1.1. Database

A computerised database will be created in which the data obtained during the study will be verified. Once the database has been debugged, the statistical analysis will be performed.

5.1.2. Database debugging

The data will be debugged before the clinical DB is closed. In section 8.1 details will be provided of this process, both those specified and agreed upon in the study's Data Management Plan and the statistical debugging performed during the analysis.

5.2. DATA ANALYSIS AND STATISTICAL TESTS

5.2.1. Changes in the planned analysis

The SAP version 1.0 of 2nd February 2018 has been modified, according an express request of the sponsor.

The following sections have been modified:

- Section 1.8, Study Design: the valid visit windows between initiation date of Pradaxa® and Visit 2 / Visit 3 have been defined
- Section 1.12, Study schedule: the dates have been modified according the real dates
- Section 3.1, Primary Objective: the valid visit windows between initiation date of Pradaxa® and Visit 2 / Visit 3 have been defined
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- Section 5.2.7, Statistical methodology: an explanatory note about the exploratory purposes of the analysis has been added.
- Section 6.1, Study population:
    - The valid VKA end date have been defined in inclusion criterion 4
    - The need of having the PACT-Q2 in all the study visits has been deleted
- Section 6.2.1 and 6.2.2, Socio-demographic data and Anthropometric data and vital signs: the p-value between males and females has been deleted in Table 2, Table 4 and Table 5.
- Section 6.2.1, Socio-demographic data: a categorisation about age (≤65 or >65 years) has been added in Table 2.
- Section 6.2.6, Scales: the number of section 6.2.6.3 has been updated.
- Section 6.2.6.3, PACT-Q2 Questionnaire at Baseline: the title of the section and the title of Table 15, Table 16 and Table 17 have been changed, adding “at Baseline”.
- Section 6.3.1, Treatment with Pradaxa®: the header cells have been changed, deleting the specification of the period days in each visit.
- Section 6.3.2.1, PACT-Q2 Questionnaire at Follow-up: the title of the section has been changed, adding “at Follow-up”.
- Section 0, Analysis of the Secondary endpoints:
    - A categorisation about age (≤65 or >65 years) has been added in Table 26.
    - The reference to the Thromboembolic risk (CHA2DS2-VASc) section has been updated in Table 26.
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- Section 8.2, Reasons for Discontinuing Pradaxa®: the header cells have been changed, deleting the specification of the period days in each visit.

5.2.2. Samples for analysis

The analyses will be performed on a single sample of assessable patients (eligible patients terminology is used in the Study Protocol), which will include all patients who meet the selection criteria.

5.2.3. Analysis of the primary endpoint

The description of patients' perception of their treatment for NVAF will be achieved using the PACT-Q2 questionnaire.

For this, comparisons of paired samples (Student's paired t-test or the non-parametric Wilcoxon signed-rank test for data without a normal distribution) will be used to compare the scores obtained in the final assessment (continuation period) to those from the baseline assessment. Additional comparisons will be performed on the scores obtained in the intermediate assessment (initial period) in comparison to the baseline assessment, and the scores obtained in the final assessment in comparison to the intermediate assessment.

For the analysis of the primary endpoint, the instructions described below will be followed:

- Patients with a VKA end date before V1 date: patients who had the Pradaxa® initiation date (the date after VKA end date) within 7 days before V1 date, will be included in the corresponding analyses V1 vs V2 and/or V1 vs V3 and/or V2 vs V3, provided the new visit windows for V2 and/or V3 are met*.
- Patients with Pradaxa® initiation date (the date after VKA end date) = V1 date: all patients will be included in the corresponding analyses (V1 vs V2 and/or V1 vs V3 and/or V2 vs V3),provided the new visit windows for V2 and/or V3 are met*
- Patients with Pradaxa® initiation date (the date after VKA end date) after V1 date: all patients will be included in the corresponding analyses (V1 vs V2 and/or V1 vs V3 and/or V2 vs V3), provided the new visit windows for V2 and/or V3 are met*

* The acceptance windows days for visit 2 and visit 3 will be the following:

  - V2 date - Day after VKA end date= 7-124 days
  - V3 date - Day after VKA end date= 125-365 days

(NOTE: Due to Pradaxa® initiation date was not recorded in the eCRF, it is assumed that the initiation date of Pradaxa® is the day after the VKA end date)

These analyses will be performed based on the actual anticoagulant treatment received by the patients (i.e. “as-treated” analysis), so that patients who discontinue the initial anticoagulant treatment at the time of an assessment will be excluded from all analyses where data from that assessment is included.

5.2.4. Analysis of the secondary endpoints

The patient population in Spain will be characterised by describing the following variables:

- Age
- Sex
- CHA2DS2-VASc score
- HAS-BLED score
- Kidney function (creatinine clearance)
- Risk factors associated with stroke and/or haemorrhage in the medical history and baseline period
- Comorbidities
- Concomitant medication
- Duration of previous treatment with VKAs
- Reasons for changing the dose of Pradaxa® or discontinuing Pradaxa®/VKAs.
- Pradaxa® dose

5.2.6. Safety analysis

The safety analyses will include all patients participating in the study who actually receive follow-up (patients for whom we have follow-up data). The statistical analyses and reporting of AEs will be descriptive in nature, based on BI standards and will focus on adverse reactions to a medication (i.e., AEs related to the anticoagulant treatment).

The safety analysis will be based on the concept of adverse events that arise during treatment. AEs that worsen with the treatment will also be deemed to "arise during treatment". AEs that appear before the first study visit or after the end of the 7-month follow-up period (the 6 months of the study + 30 days follow-up) will not be deemed to have arisen during treatment and will not be included in the summary tables.

The safety analyses will focus on the following parameters:

- Adverse reactions to the medication
- Adverse reactions to the medication that cause the anticoagulant treatment to be discontinued
- Serious adverse reactions to the medication

- Deaths
- SAEs

5.2.7. Statistical methodology

Categorical variables will be described by their absolute and relative frequencies. Continuous variables will be described using the mean and 95% confidence interval (95% CI), standard deviation, median, 25th and 75th percentiles, minimum and maximum, including the total number of valid values.

For the comparisons between visits for quantitative variables, parametric tests (Student's paired t-test) or non-parametric tests (Wilcoxon signed-rank test) shall be used, according to the characteristics of the variables in question.

A level of statistical significance of 0.05 will be applied in all the statistical tests.

The data will be statistically analysed using the SAS statistical package, version 9.4 or later.

Due to the nature of this non-interventional study, there is no (confirmatory) hypothesis testing foreseen in a strict statistical sense. Analyses are descriptive in nature and confidence intervals and p-values from statistical models are used for exploratory purposes.

5.2.8. Data processing

The statistical analysis will be performed on the available data from assessable patients.

Missing data or lost values will not be imputed so as not to introduce information bias. We hope to avoid having missing data for important variables by controlling with filters when collecting data from the eCRF. Missing data on secondary endpoints, or those of lesser importance, will not affect the sample size or the outcome of the primary objective. For categorical variables, percentages will be calculated taking into account the data available, and for quantitative variables the "valid N" will be shown.

Where quantitative variables are transformed to meet normality criteria in those multivariate models requiring it, the results will be shown using the original scale. Quantitative or qualitative data may be re-codified if required for analysis.

6. RESULTS

6.1. STUDY POPULATION

6.1.1. Recruited and assessable patients

In accordance with the study protocol, we plan to enrol approximately 1087 patients to participate in the study, thanks to the cooperation of physicians at 200 cardiology or non-specialist centres in four autonomous communities in Spain.

The following table will describe the total number of assessable patients and the exclusion/inclusion criteria according to which others will be classified as non-assessable.

The following criteria will be verified:

- Inclusion criterion 1. Granting informed consent in writing prior to enrolment *Patients for whom we do not have a date of signature of the informed consent or for whom this is after the date of enrolment in the study will be excluded*.
- Inclusion criterion 2. Patients of both sexes ≥ 18 years of a age with a diagnosis of NVAF. *Patients less than 18 years of age or whose age is not stated will be excluded. The diagnosis of NVAF is not assessable based on the data reported in the eCRF.*
- Inclusion criterion 3. Patients treated continuously with VKAs for stroke prophylaxis for at least six months prior to the baseline visit. *Patients for whom we do not have dates for the start and end of treatment with VKAs (month and year as a minimum) or patients who have not been undergoing treatment for at least six months will be excluded*.
- Inclusion criterion 4. Patients switching to treatment with Pradaxa® in accordance with the recommendations of the competent health authorities described in the therapeutic positioning report for NOACs and the authorisations of the various autonomous communities. *Follow-up of the recommendations of the therapeutic positioning report for NOACs is not assessable based on the data reported in the eCRF.*
- Exclusion criterion 1. Contraindications for the use of Pradaxa® or VKAs described in the Summary of Product Characteristics (SmPC). *Not assessable from data reported in the eCRF*.
- Exclusion criterion 2. Patients receiving Pradaxa® or VKAs for any reason other than stroke prophylaxis in NVAF. *Not assessable from data reported in the eCRF*.

- Exclusion criterion 3. Participation in any clinical trial of an investigational medicinal product or medical device. *Not assessable from data reported in the eCRF*.

For the criteria that are not assessable from data reported in the eCRF, patients in whom the investigator indicates criterion non-compliance in the "Selection criteria" section of the eCRF will be excluded.

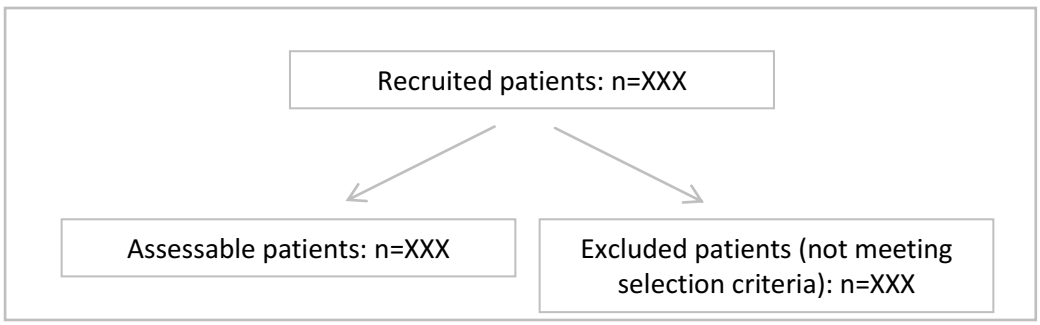
Table 1. Recruited and assessable patients

	n (%)
Patients recruited	
Non-assessable patients	
Patients who have not granted informed consent in writing prior to enrolment	
Patients under 18 years of age or not diagnosed with NVAF	
Patients who have not been treated continuously with VKAs for stroke prophylaxis for at least six months prior to the baseline visit	
Patients who were not switching to Pradaxa	
Patients receiving Pradaxa® or VKAs for any reason other than stroke prophylaxis in NVAF	
Patients with contraindications for the use of Pradaxa® or VKAs described in the Summary of Product Characteristics (SmPC)	
Patients who are participating in any clinical trial of an investigational medicinal product or medical device	
Assessable patients	
Patients for the safety sample[1]	

Note: A single patient may simultaneously be classified as non-assessable for more than one reason.
[1] *All patients participating in the study with follow-up data*

The figure below is a flow diagram of study patients, which will indicate the number of recruited and assessable patients, as well as the number of patients excluded from the study.

Figure 1. Flow diagram of patients



6.2. DESCRIPTION OF THE SAMPLE AT BASELINE

6.2.1. Socio-demographic data

This section will describe the socio-demographic data of the patients in the study.

Figure 2. Distribution of the sex of patients
(Pie chart: Male/Female)

Table 2. Age of patients (years)	
	Total
Age (years)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	
Age in categories	
≤65 years	
>65 years	

Figure 3. Distribution of patient ages
(Pie chart: ≤ 65 years / > 65 years)

Table 3. Description of race	
	n (%)
Race	
Caucasian	
North African	
Sub-Saharan African	
Afro-American	
Latin American	
Asian	
Other	
…	

Figure 4. Distribution of patients by AC

(Map: Catalonia/Galicia/Andalusia/Basque Country)

6.2.2. Anthropometric data and vital signs

This section will describe the data related to anthropometric characteristics and vital signs at the time of the baseline visit.

Table 4. Anthropometric characteristics

	Total		
Weight (kg)			
Mean (SD)			
95% CI			
Median (P25; P75)			
(Min; Max)			
Valid N			
Height (cm)			
Mean (SD)			
95% CI			
Median (P25; P75)			
(Min; Max)			
Valid N			
BMI (kg/m^2)			
Mean (SD)			
95% CI			
Median (P25; P75)			
(Min; Max)			
Valid N			

Table 5. Vital signs	
Total	
Heart rate (bpm)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	
Systolic blood pressure (mmHg)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	
Diastolic blood pressure (mmHg)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	

6.2.3. Medical history

This section will describe the medical history data of the patients participating in the study.

Table 6. Clinically relevant disease and/or surgery			
	n	**%[1]**	**%[2]**
Clinically relevant disease and/or surgery			
Yes			--
No			--
Type of disease and/or surgery			
Ischaemic stroke			
Episodes of bleeding, anaemia or predisposition to bleeding			
Arterial thromboembolisms outside of the CNS			
Diabetes mellitus			
Hypertension			
Hyperlipidaemia			

Table 6. Clinically relevant disease and/or surgery			
	n	**%[1]**	**%[2]**
Stable angina pectoris			
Acute Coronary Syndrome. ST-segment elevation myocardial infarction (ACS-STEMI)			
Acute Coronary Syndrome. Non-ST-segment elevation myocardial infarction (ACS-NSTEMI)			
Acute Coronary Syndrome (ACS). Unstable angina			
Peripheral arterial disease			
Procedure performed in vascular disease (last episode) or bypass			
Congestive heart failure			
Left ventricular dysfunction			
Abdominal aortic aneurysm			
Aortic plaque			
Kidney failure (chronic dialysis, kidney transplant or creatinine ≥ 2.26 mg/dl)			
Liver failure (cirrhosis or biochemical data indicative of liver impairment, bilirubin > 2 x ULN, AST/ALT > 3 x ULN)			
Vascular disease			
Alcoholism			
≥ 8 alcoholic drinks per week (% around n=XX)			
< 8 alcoholic drinks per week (% around n=XX)			
Known unstable INR (time in therapeutic range < 60% by the direct method or < 65% by the Rosendaal method)			
Others			
...			
...			
...			

[1] *Percentages calculated based on the total number of assessable patients (n=XX)*
[2] *Percentages calculated based on the total number of patients with a history of clinically relevant disease and/or surgery (n=XX)*
Note: A single patient may simultaneously specify more than one disease and/or surgery

6.2.4. Creatinine clearance

This section will describe the serum creatinine values taken from the last blood test, as well as creatinine clearance values.

Table 7. Serum creatinine and creatinine clearance	
	Total
Serum creatinine (mg/dl)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	
Creatinine clearance (Cockcroft-Gault) (ml/min) *	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	

** Cockcroft-Gault= ((140-age) X Weight (kg))/ (72 X creatinine (mg/dl))*0.85 (if female)*

Patients will also be classified by disease stage based on their Cockcroft-Gault values (ml/min):

Table 8. Stages of kidney disease based on creatinine clearance	
	n (%)
Stages of kidney disease (based on Cockcroft-Gault)	
No kidney failure (> 80 ml/min)	
Mild kidney failure (50-80 ml/min)	
Moderate kidney failure (30-49 ml/min)	
Severe kidney failure (15-29 ml/min)	
End-stage kidney failure/dialysis (< 15 ml/min)	

6.2.5. Treatment

6.2.5.1 VKA treatment

This section will describe the data on previous anticoagulant treatment with VKAs.

Table 9. Previous VKA treatment			
	n (%)	Duration (months) Mean (SD)	Dose (mg/day) Mean (SD)
Active substance of the VKA[1] and treatment duration			
Acenocoumarol			
Warfarin			
Others			
….			
….			

[1] *A single patient may simultaneously specify more than one active substance*

6.2.5.2 Pradaxa® treatment

This section will describe the reasons for switching from VKAs to Pradaxa®, as well as the prescribed dose.

Table 10. Reasons for switching from VKAs to Pradaxa®	
	n (%)
Reason[1] triggering the switch from VKAs to Pradaxa®	
Hypersensitivity to the drug	
Patients with a history of intracranial haemorrhage (ICH) (except during the acute phase) in whom the benefits of anticoagulation are deemed to outweigh the risk of haemorrhage.	
Patients with ischaemic stroke who present clinical and neuroimaging criteria indicating a high risk of ICH	
Patients undergoing treatment with VKAs, suffering from severe arterial thromboembolic episodes despite good INR control.	
Patients who have started treatment with VKAs in whom it is not possible to keep the INR in range (2-3) despite good therapeutic compliance.	
Lack of access to conventional INR management	
Patient's decision	
Others	
…	
Unknown	

[1] *A single patient may simultaneously specify more than one reason*

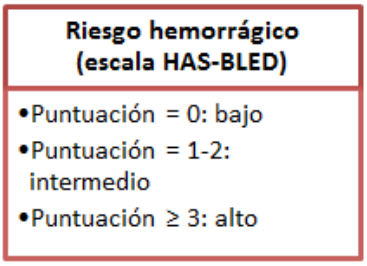
Figure 5. Pradaxa® dose

(Pie chart: 110 mg / 150 mg)

6.2.6. Scales

6.2.6.1 HAS-BLED scale

This section will describe the scores obtained on the HAS-BLED scale and the corresponding haemorrhagic risk levels.



Riesgo hemorrágico (escala HAS-BLED)	Haemorragic risk (HAS-BLED scale)
Puntuación	Score
bajo	low
intermedio	intermediate
alto	high

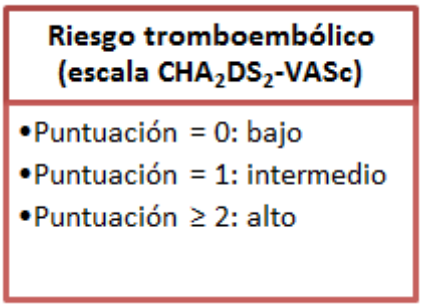
Table 11. HAS-BLED scale

	n (%)
HAS-BLED scale	
Uncontrolled hypertension with SBP ≥ 160 mmHg	
Kidney failure	
Liver failure	
History of stroke	
History of bleeding, anaemia or predisposition to bleeding	
Unstable/high or poor INR (<60% of time within therapeutic range)	
Age > 65 years	
Medications that affect haemostasis	
Consumptions of ≥ 8 alcoholic drinks per week	

Table 12. HAS-BLED scale score and haemorrhagic risk
HAS-BLED score
Mean (SD)
95% CI
Median (P25; P75)
(Min; Max)
Valid N
Haemorrhagic risk based on the HAS-BLED scale *n (%)*
Low risk
Intermediate risk
High Risk

6.2.6.2 CHA2DS2-VASc classification

This section will describe the scores obtained on the CHA_2DS_2-VASc scale and the corresponding thromboembolic risk levels.



Riesgo tromboembólico (escala CHA_2DS_2-VASc)	Thromboembolic risk (CHA_2DS_2-VASc scale)
Puntuación	Score
bajo	low
intermedio	intermediate
alto	high

Table 13. CHA_2DS_2-VASc scale	
	n (%)
CHA2DS2-VASc scale	
Congestive heart failure/left ventricular dysfunction	
Hypertension	
Age ≥ 75 years	
Diabetes mellitus	
Stroke/TIA/thromboembolism	
Vascular disease (history of myocardial infarction, peripheral artery disease or aortic plaque)	
Age 65-74 years	
Female sex	

Table 14. CHA2DS2-VASc scale and thromboembolic risk	
CHA2DS2-VASc scale score	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
Valid N	
Thromboembolic risk based on the CHA2DS2-VASc scale *n (%)*	
Low risk	
Intermediate risk	
High Risk	

6.2.6.3 PACT-Q2 Questionnaire at Baseline

This section will describe the items in the PACT-Q2 questionnaire and the scores obtained for the respective domains.

Table 15. PACT-Q2 Questionnaire at Baseline (I)

CONVENIENCE	Not at all n (%)	A little bit n (%)	Moderately n (%)	A lot n (%)	A great deal n (%)
B1. In what way do you find it difficult to take your anticoagulant treatment (because they are pills or injections, because of the number you have to take or how often you have to take them, etc.)?					
B2. To what extent do you find it bothersome to take your anticoagulant treatment?					
B3. Do you sometimes need to adjust the dose of some anticoagulant treatments? Does this cause you any difficulties?					
B4. There are certain types of medication that CANNOT BE TAKEN while you are on anticoagulant treatment. Does this cause you any difficulties?					
B5. You are advised to avoid certain foods while on anticoagulant treatment. Does this cause you any difficulties?					
B6. To what extent do you find it difficult to take your anticoagulant treatment when you are not at home?					
B7. To what extent do you find it difficult to organise your time around your anticoagulant treatment (appointments with nurses, doctors, laboratories, etc.)?					
B8. To what extent do you find the medical follow-up required for your anticoagulant treatment bothersome?					
B9. To what extent do you find it difficult to take the anticoagulant treatment regularly following your doctor's instructions?					
B10. Do you feel that you are more dependent on others (your partner,					

Table 15. PACT-Q2 Questionnaire at Baseline (I)

CONVENIENCE	Not at all n (%)	A little bit n (%)	Moderately n (%)	A lot n (%)	A great deal n (%)
family, nurse, etc.) due to your anticoagulant treatment? B11. To what extent does having to interrupt or discontinue your anticoagulant treatment worry you?					
C1. Are your day-to-day activities (work, leisure, social events, physical activities, etc.) limited due to the potential side effects of the treatment (small bruises, bleeding, etc.)? C2. How much physical discomfort do the bruises or pain cause?					

Table 16. PACT-Q2 Questionnaire at Baseline (II)

SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	Not at all	**A little bit**	**To some extent/moderately**	**A lot**	**Completely**
D1. To what extent do you feel more at ease thanks to your anticoagulant treatment? D2. Do you think that the anticoagulant treatment you are taking has been able to reduce your symptoms (pain or swelling in the legs, palpitations, shortness of breath, chest pain, etc.)?					
	They are much worse than I expected	**They are worse than I expected**	**They are about what I expected**	**They are better than I expected**	**They are much better than I expected**
D3. How do the side effects you have, such as small bruises or bleeding (when shaving, cooking, if you cut yourself, etc.) compare to what you expected?					

Table 16. PACT-Q2 Questionnaire at Baseline (II)					
SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	Very unsatisfactory	**Unsatisfactory**	**Neither satisfactory nor unsatisfactory**	**Satisfactory**	**Very satisfactory**
D4. With regard to the follow-up of your disease and the anticoagulant treatment you are taking, what is your degree of satisfaction with your level of independence?					
D5. What is your degree of satisfaction with the methods (appointments with nurses, doctors, laboratories, etc.) used to ensure the follow-up of your disease and anticoagulant treatment?					
D6. What is your degree of satisfaction with the presentation of your anticoagulant treatment (pill to be taken orally/injections)?					
D7. In general, what is your degree of satisfactions with your anticoagulant treatment?					

The PACT-Q2 questionnaire is made up of two domains:

- Convenience (items B1 to B7 and C1 to C2) → This domain is calculated by adding the inverted scores (6 – item score) for each of the 9 items in question, and converting to a scale from 0 to 100.
- Satisfaction with the anticoagulant treatment (items D1 to D7) → This domain is calculated by adding the scores for each of the 7 items in question, and converting to a scale from 0 to 100.

The table below will describe the scores obtained for both domains:

Table 17. PACT-Q2 Questionnaire Score at Baseline[1]

DOMAINS
Convenience
Mean (SD)
95% CI
Median (P25; P75)
(Min; Max)
Valid N
Satisfaction with the anticoagulant treatment
Mean (SD)
95% CI
Median (P25; P75)
(Min; Max)
Valid N

[1] *Range from 0 to 100*

6.3. FOLLOW-UP DATA

6.3.1. Treatment with Pradaxa®

The following section will describe those patients whose Pradaxa® regimen was changed and the reasons for that change.

Table 18. Change to the Pradaxa® treatment regimen

	Visit 2 n (%)	Visit 3 n (%)
Is the patient still receiving the same dose prescribed at the previous visit?		
Yes		
No		
New Pradaxa® dose [1]		
110 mg		
150 mg		
Reason for changing the dose of Pradaxa® [1]		
…..		
…..		

[1] *Percentage calculated from the number of patients whose dose has been changed since the previous visit (n=XX)*

The table below will describe all dose changes that have taken place during follow-up (n=XX patients with dose changes at visit 2 or visit 3):

Table 19. Dose changes during follow-up

	n (%)
PATIENTS WITH THE SAME DOSE THROUGHOUT FOLLOW-UP	
PATIENTS WITH DOSE CHANGES	
110 mg dose at visit 1	
Change to 150 mg at visit 2 and 3	
Change to 150 mg at visit 3 (110 mg at visit 2)	
Change to 150 mg at visit 2 and change to 110 mg at visit 3	
150 mg dose at visit 1	
Change to 110 mg at visit 2 and 3	
Change to 110 mg at visit 3 (150 mg at visit 2)	
Change to 110 mg at visit 2 and change to 150 mg at visit 3	

[1] *Percentages calculated from the total number of patients with dose changes at any visit during follow-up*

6.3.2. Scales

6.3.2.1 PACT-Q2 Questionnaire at Follow-up

This section will describe the items in the PACT-Q2 questionnaire and the scores obtained for the respective domains for each follow-up visit.

VISIT 2

Table 20. PACT-Q2 questionnaire - VISIT 2 (I)

CONVENIENCE	Not at all n (%)	A little bit n (%)	Moderately n (%)	A lot n (%)	A great deal n (%)
B1. In what way do you find it difficult to take your anticoagulant treatment (because they are pills or injections, because of the number you have to take or how often you have to take them, etc.)?					
B2. To what extent do you find it bothersome to take your anticoagulant treatment?					
B3. Do you sometimes need to adjust the dose of some anticoagulant treatments? Does this cause you any difficulties?					
B4. There are certain types of medication that CANNOT BE TAKEN while you are on anticoagulant treatment. Does this cause you any difficulties?					
B5. You are advised to avoid certain foods while on anticoagulant treatment. Does this cause you any difficulties?					
B6. To what extent do you find it difficult to take your anticoagulant treatment when you are not at home?					
B7. To what extent do you find it difficult to organise your time around your anticoagulant treatment (appointments with nurses, doctors, laboratories, etc.)?					
B8. To what extent do you find the medical follow-up required for your anticoagulant treatment bothersome?					
B9. To what extent do you find it difficult to take the anticoagulant					

Table 20. PACT-Q2 questionnaire - VISIT 2 (I)					
CONVENIENCE	**Not at all** n (%)	**A little bit** n (%)	**Moderately** n (%)	**A lot** n (%)	**A great deal** n (%)
treatment regularly following your doctor's instructions? B10. Do you feel that you are more dependent on others (your partner, family, nurse, etc.) due to your anticoagulant treatment? B11. To what extent does having to interrupt or discontinue your anticoagulant treatment worry you?					
C1. Are your day-to-day activities (work, leisure, social events, physical activities, etc.) limited due to the potential side effects of the treatment (small bruises, bleeding, etc.)? C2. How much physical discomfort do the bruises or pain cause?					

Table 21. PACT-Q2 questionnaire - VISIT 2 (II)					
SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	Not at all	**A little bit**	**To some extent/moderately**	**A lot**	**Completely**
D1. To what extent do you feel more at ease thanks to your anticoagulant treatment? D2. Do you think that the anticoagulant treatment you are taking has been able to reduce your symptoms (pain or swelling in the legs, palpitations, shortness of breath, chest pain, etc.)?					

Table 21. PACT-Q2 questionnaire - VISIT 2 (II)					
SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	They are much worse than I expected	**They are worse than I expected**	**They are about what I expected**	**They are better than I expected**	**They are much better than I expected**
D3. How do the side effects you have, such as small bruises or bleeding (when shaving, cooking, if you cut yourself, etc.) compare to what you expected?					
	Very unsatisfactory	**Unsatisfactory**	**Neither satisfactory nor unsatisfactory**	**Satisfactory**	**Very satisfactory**
D4. With regard to the follow-up of your disease and the anticoagulant treatment you are taking, what is your degree of satisfaction with your level of independence? D5. What is your degree of satisfaction with the methods (appointments with nurses, doctors, laboratories, etc.) used to ensure the follow-up of your disease and anticoagulant treatment? D6. What is your degree of satisfaction with the presentation of your anticoagulant treatment (pill to be taken orally/injections)? D7. In general, what is your degree of satisfactions with your anticoagulant treatment?					

VISIT 3

Table 22. PACT-Q2 questionnaire - VISIT 3 (I)

CONVENIENCE	Not at all n (%)	A little bit n (%)	Moderately n (%)	A lot n (%)	A great deal n (%)
B1. In what way do you find it difficult to take your anticoagulant treatment (because they are pills or injections, because of the number you have to take or how often you have to take them, etc.)?					
B2. To what extent do you find it bothersome to take your anticoagulant treatment?					
B3. Do you sometimes need to adjust the dose of some anticoagulant treatments? Does this cause you any difficulties?					
B4. There are certain types of medication that CANNOT BE TAKEN while you are on anticoagulant treatment. Does this cause you any difficulties?					
B5. You are advised to avoid certain foods while on anticoagulant treatment. Does this cause you any difficulties?					
B6. To what extent do you find it difficult to take your anticoagulant treatment when you are not at home?					
B7. To what extent do you find it difficult to organise your time around your anticoagulant treatment (appointments with nurses, doctors, laboratories, etc.)?					
B8. To what extent do you find the medical follow-up required for your anticoagulant treatment bothersome?					
B9. To what extent do you find it difficult to take the anticoagulant treatment regularly following your doctor's instructions?					
B10. Do you feel that you are more dependent on others (your partner, family, nurse, etc.) due to your anticoagulant treatment?					
B11. To what extent does having to interrupt or discontinue your					

Table 22. PACT-Q2 questionnaire - VISIT 3 (I)					
CONVENIENCE	**Not at all** n (%)	**A little bit** n (%)	**Moderately** n (%)	**A lot** n (%)	**A great deal** n (%)
anticoagulant treatment worry you?					
C1. Are your day-to-day activities (work, leisure, social events, physical activities, etc.) limited due to the potential side effects of the treatment (small bruises, bleeding, etc.)? C2. How much physical discomfort do the bruises or pain cause?					

Table 23. PACT-Q2 questionnaire - VISIT 3 (II)					
SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	Not at all	**A little bit**	**To some extent/moderately**	**A lot**	**Completely**
D1. To what extent do you feel more at ease thanks to your anticoagulant treatment? D2. Do you think that the anticoagulant treatment you are taking has been able to reduce your symptoms (pain or swelling in the legs, palpitations, shortness of breath, chest pain, etc.)?					
	They are much worse than I expected	**They are worse than I expected**	**They are about what I expected**	**They are better than I expected**	**They are much better than I expected**
D3. How do the side effects you have, such as small bruises or bleeding (when shaving, cooking, if you cut yourself, etc.) compare to what you expected?					

Table 23. PACT-Q2 questionnaire - VISIT 3 (II)					
SATISFACTION WITH THE ANTICOAGULANT TREATMENT	n (%)	n (%)	n (%)	n (%)	n (%)
	Very unsatisfactory	**Unsatisfactory**	**Neither satisfactory nor unsatisfactory**	**Satisfactory**	**Very satisfactory**
D4. With regard to the follow-up of your disease and the anticoagulant treatment you are taking, what is your degree of satisfaction with your level of independence?					
D5. What is your degree of satisfaction with the methods (appointments with nurses, doctors, laboratories, etc.) used to ensure the follow-up of your disease and anticoagulant treatment?					
D6. What is your degree of satisfaction with the presentation of your anticoagulant treatment (pill to be taken orally/injections)?					
D7. In general, what is your degree of satisfactions with your anticoagulant treatment?					

The table below will describe the scores obtained in the 2 domains of the PACT-Q2 questionnaire at both time points during follow-up:

Table 24. PACT-Q2 questionnaire score[1] during follow-up		
DOMAINS	**Visit 2**	**Visit 3**
Convenience		
Mean (SD)		
95% CI		
Median (P25; P75)		
(Min; Max)		
Valid N		
Satisfaction with the anticoagulant treatment		
Mean (SD)		
95% CI		
Median (P25; P75)		
(Min; Max)		
Valid N		

[1] *Range from 0 to 100*

6.4. ANALYSIS OF THE PRIMARY ENDPOINT: PERCEPTION OF TREATMENT FOR NVAF USING THE PACT-Q2 QUESTIONNAIRE

This section will analyse the primary objective of the study, which is to describe patients' perception of their treatment for NVAF using the PACT-Q2 questionnaire at three time points: during the baseline period after the indication for Pradaxa®, after approximately one month and during the continuation period.

For the analysis of the primary endpoint, the instructions described in section 5.2.3 will be followed.

6.4.1. PACT-Q2 questionnaire scores during follow-up

Table 25. Evolution of PACT-Q2 questionnaire scores

DOMAINS	Visit 1	Visit 2	Visit 3	p[1]
COMPARISONS for VISIT 1 *vs* VISIT 2				
Convenience (range from 0 to 100)				
Mean (SD)		--		
95% CI		--		
Median (P25; P75)		--		
(Min; Max)		--		
Valid N		--		
Satisfaction with anticoagulant treatment (range from 0 to 100)				
Mean (SD)		--		
95% CI		--		
Median (P25; P75)		--		
(Min; Max)		--		
Valid N		--		
COMPARISONS for VISIT 1 *vs* VISIT 3				
Convenience (range from 0 to 100)				
Mean (SD)			--	
95% CI			--	
Median (P25; P75)			--	
(Min; Max)			--	
Valid N			--	
Satisfaction with anticoagulant treatment (range from 0 to 100)				
Mean (SD)			--	

Table 25. Evolution of PACT-Q2 questionnaire scores				
DOMAINS	**Visit 1**	**Visit 2**	**Visit 3**	**p[1]**
95% CI			--	
Median (P25; P75)			--	
(Min; Max)			--	
Valid N			--	
COMPARISONS for VISIT 2 *vs* VISIT 3				
Convenience (range from 0 to 100)				
Mean (SD)	--			
95% CI	--			
Median (P25; P75)	--			
(Min; Max)	--			
Valid N	--			
Satisfaction with anticoagulant treatment (range from 0 to 100)				
Mean (SD)	--			
95% CI	--			
Median (P25; P75)	--			
(Min; Max)	--			
Valid N	--			

[1] *Student's t-test or Wilcoxon test*

NOTE: Patients without dates in range in each visit, will be excluded of the comparisons involved

Figure 6. Evolution of PACT-Q2 questionnaire scores

(Line graph for the 2 domains at the 3 study time points)

6.5. ANALYSIS OF THE SECONDARY ENDPOINTS: PATIENT CHARACTERISATION

This section will analyse the study's secondary objective, which is the characterisation of patients based on:

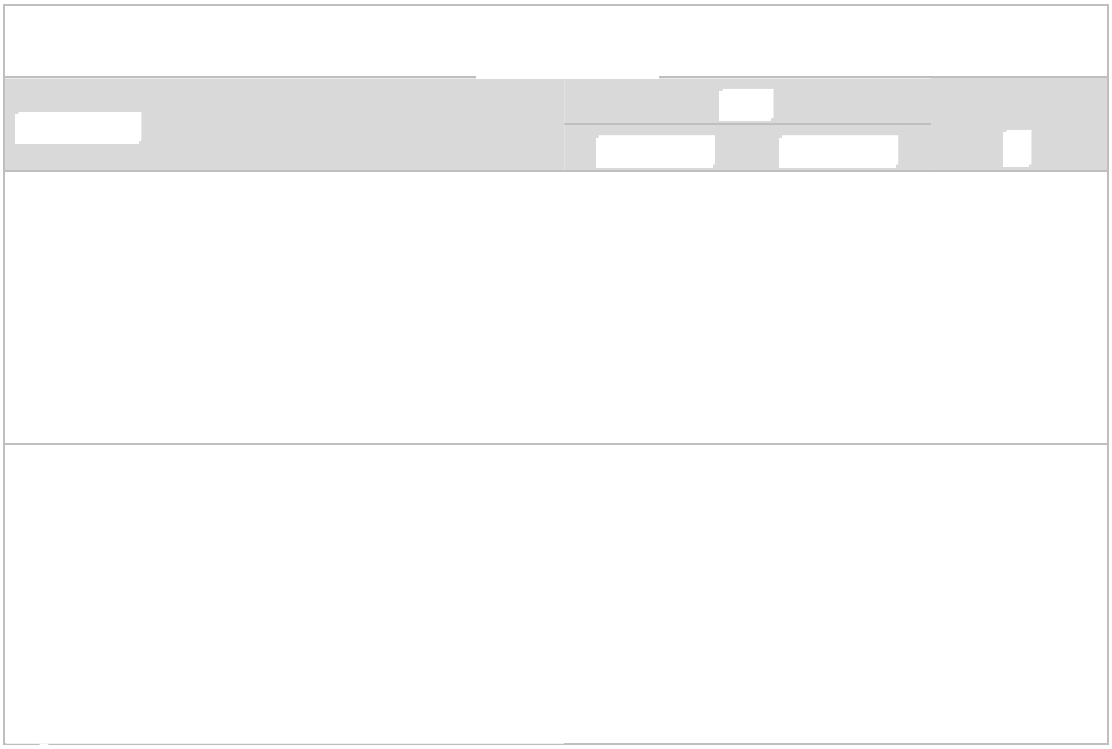
- Socio-demographic data
- Haemorrhagic risk (HAS-BLED) and thromboembolic risk (CHA_2DS_2-VASc)
- Kidney function
- Risk factors associated with stroke and/or haemorrhage
- Comorbidities and concomitant medications
- Treatment: previous treatment with VKAs and Pradaxa® dose

Patient characterisation will be described for the entire sample as well as by dose (Figure 5.).

Table 26. Patient characterisation

	Total n (%)	**n (%)**	**n (%)**
Socio-demographic data			
Sex			
Male			
Female			
Age (n, (mean±SD))			
≤65 years			
>65 years			
Haemorrhagic risk and thromboembolic risk			
Haemorrhagic risk (HAS-BLED) (*see section 6.2.6.1)*			
Low risk			
Intermediate risk			
High Risk			
Thromboembolic risk (CHA_2DS_2-VASc) *(see section 6.2.6.2)*			
Low risk			
Intermediate risk			
High Risk			
Kidney function *(see section 6.2.4)*			
Serum creatinine (mg/dl)			
Creatinine clearance (ml/min) (Cockcroft-Gault)			

Table 26. Patient characterisation			
	Total n (%)	n (%)	n (%)
Stages of kidney disease (based on Cockcroft-Gault)			
No kidney failure (> 80 ml/min)			
Mild kidney failure (50-80 ml/min)			
Moderate kidney failure (30-49 ml/min)			
Severe kidney failure (15-29 ml/min)			
End-stage kidney failure/dialysis (< 15 ml/min)			
History of stroke			
Yes			
No			
History of bleeding, anaemia or predisposition to bleeding			
Yes			
No			
Comorbidities *(see section 6.2.3 and annex 8.3)*			
Yes			
No			
Concomitant medications *(see section 6.8)*			
Yes			
No			
Previous treatment with VKAs *(see sections 6.2.5.1 and 6.2.5.2)*			
Duration (months)			
Acenocoumarol			
Warfarin			
Dose (mg/day)			
Acenocoumarol			
Warfarin			
Treatment with Pradaxa® *(see sections 6.2.5.2 and 6.3.1)*			
Dose			
110 mg			--
150 mg		--	
Pradaxa® discontinued during follow-up			
Yes			
No			



6.7. SAFETY ANALYSIS

This section will describe the adverse events reported by patients (see safety sample, Table 1) during the course of the study.

Table 55. Presence of adverse events	
	n (%)
AVAILABLE PATIENTS [1]	
No adverse events	
SERIOUS adverse events	
ASSOCIATED with the study treatment [2]	
NOT ASSOCIATED with the study treatment (ARs) [2]	
NON-SERIOUS adverse events	
ASSOCIATED with the study treatment [2]	
NOT ASSOCIATED with the study treatment (ARs)	

[1] *All patients participating in the study with follow-up data*
[2] *These AEs will be described in more detail in the following sections*

The following sections will describe all the adverse events associated with the study treatment (ARs), as well as the serious adverse events not associated with the study treatment (including deaths).

6.7.1. Adverse reactions to the medication

The table below will describe the data relating to adverse reactions (ARs) to a medication, i.e. AEs associated with the anticoagulant treatment.

Table 56. Adverse reactions to the medication	
	n (%)[1]
AVAILABLE PATIENTS [2]	
Patients with ARs [3]	
Patients with ARs leading to discontinuation of the anticoagulant treatment	
Patients with serious ARs	
Patients without ARs	

[1] *All percentages are calculated based on the total number of available patients (n=XX)*
[2] *All patients participating in the study with follow-up data*
[3] *A single patient may be classified in both categories: ARs leading to discontinuation of the treatment and serious ARs*

6.7.2. Serious adverse events

The table below will describe the data relating to serious adverse events (SAEs), regardless of whether they are associated with the study treatment.

Table 57. Presence of adverse events (including deaths)	
	n (%)[1]
AVAILABLE PATIENTS [2]	
Patients with SAEs	
Associated with the study treatment	
Not associated with the study treatment	
Patients without SAEs	

[1] All percentages are calculated based on the total number of available patients (n=XX)
[2] All patients participating in the study with follow-up data

6.7.3. Deaths

The table below will describe the deaths recorded during the study, regardless of whether they are associated with the study treatment.

Table 58. Recorded deaths	
	n (%)[1]
AVAILABLE PATIENTS [2]	
Patients having died during the study	
Associated with the study treatment	
Not associated with the study treatment	
Patients remaining alive during the study	

[1] All percentages are calculated based on the total number of available patients (n=XX)
[2] All patients participating in the study with follow-up data

6.7.4. Description of the characteristics of adverse events associated with the study treatment and serious adverse events not associated with the study treatment

This section will describe the characteristics of all adverse events associated with the study treatment (ARs), as well as serious adverse events (SAEs) not associated with the study treatment (including deaths): seriousness, association with the study treatment, action taken and outcome.

Table 59. Description of ARs and SAEs not associated with the study treatment																				
Description of ARs/SAEs	**n[1]**	**%[2]**	**n[3]**	**Intensity**			**Association with the study treatment**		**Action taken with the investigational medicinal product**							**Outcome**				
				1	**2**	**3**	**Yes**	**No**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**3**	**4**	**5**
XX system disorders																				
YY system disorders																				
…																				
Total number of patients with ARs/SAEs			-																	
Total number of ARs/SAEs	-	-																		

[1] Number of patients with ARs/SAEs

[2] Percentage of patients with ARs/SAEs with regard to the total number of patients available for the safety sample (n=XX)

[3] Number of ARs/SAEs

Intensity: 1. Mild / 2. Moderate / 3. Serious; **Serious:** 1. Yes / 2. No; **Association with the investigational medicinal product:** 1. Probable / 2. Possible / 3. No association; **Action taken with the study treatment:** 1. Continue / 2. Reduce / 3. Discontinue / 4. Increase / 5. Complete in accordance with the protocol / 6. Discontinue and reintroduce / 7. Not applicable; **Outcome:** 1. Recovered / 2. Not yet recovered / 3. Sequelae / 4. Fatal / 5. Unknown

In addition, annex 8.4 will include a detailed list of each of these adverse events associated with the study treatment (ARs), as well as serious adverse events (SAEs) not associated with the study treatment (including deaths).

6.8. CONCOMITANT MEDICATION

This section will describe the data relating to pharmacological treatments used concomitantly with the anticoagulant treatment during the study, for the entire samples (Figure 5.).

Table 60. Concomitant medication

	Total								
	n	%[1]	%[2]	n	%[1]	%[2]	n	%[1]	%[2]
Concomitant medication									
Yes									--
No									--
Type of concomitant medication									
Type 1									
Type 2									
…									

[1] *Percentages calculated based on the total number of assessable patients (n=XX)*
[2] *Percentage calculated based on the total number of patients taking concomitant medication (n=XX)*
Note: A single patient may simultaneously specify more than one concomitant medication

7. CONCLUSIONS

8. ANNEXES

8.1. ANNEX 1. DB DEBUGGING

This section will include the debugging process carried out on the study's clinical database, established in the Data Management Plan. It will also include a description of the debugging carried out during the statistical analysis.

8.2. ANNEX 2. REASONS FOR DISCONTINUING PRADAXA®

This section will list the reasons for which patients have discontinued Pradaxa® at any follow-up visit (n_{VISIT2}=XX and n_{VISIT3}=XX) according to Figure 1. .

Table 61. Continuation with Pradaxa® treatment

	Visit 2 n (%)	Visit 3 n (%)
PATIENTS NOT RECEIVING THE SAME TREATMENT		
Reason for no longer receiving Pradaxa® treatment		
…..		
…..		

8.3. ANNEX 3. MEDICAL HISTORY

Table 62. Clinically relevant disease and/or surgery

	Total								
	n	%[1]	%[2]	n	%[1]	%[2]	n	%[1]	%[2]
Clinically relevant disease and/or surgery									
Yes									--
No									--
Type of disease and/or surgery									
Ischaemic stroke									
Episodes of bleeding, anaemia or predisposition to bleeding									
Arterial thromboembolisms outside of the CNS									
Diabetes mellitus									
Hypertension									
Hyperlipidaemia									
Stable angina pectoris									
Acute Coronary Syndrome. ST-segment elevation myocardial infarction (ACS-STEMI)									
Acute Coronary Syndrome. Non-ST-segment elevation myocardial infarction (ACS-NSTEMI)									
Acute Coronary Syndrome (ACS). Unstable angina									
Peripheral arterial disease									
Procedure performed in vascular disease (last episode) or bypass									
Congestive heart failure									
Left ventricular dysfunction									

Table 62. Clinically relevant disease and/or surgery

	Total								
	n	%[1]	%[2]	n	%[1]	%[2]	n	%[1]	%[2]
Abdominal aortic aneurysm									
Aortic plaque									
Kidney failure (chronic dialysis, kidney transplant or creatinine ≥ 2.26 mg/dl)									
Liver failure (cirrhosis or biochemical data indicative of liver impairment, bilirubin > 2 x ULN, AST/ALT > 3 x ULN)									
Vascular disease									
Alcoholism									
≥ 8 alcoholic drinks per week (% around n=XX)									
< 8 alcoholic drinks per week (% around n=XX)									
Known unstable INR (time in therapeutic range < 60% by the direct method or < 65% by the Rosendaal method)									
Others									
...									
...									
...									

[1] *Percentages calculated based on the total number of assessable patients (n=XX)*
[2] *Percentages calculated based on the total number of patients with a history of clinically relevant disease and/or surgery (n=XX)*
Note: A single patient may simultaneously specify more than one disease and/or surgery

8.4. ANNEX 4. DETAILS OF REPORTED ARs AND SAEs

This section will include the list of patients with adverse events associated with the study treatment (ARs), as well as serious adverse events (SAEs) not associated with the study treatment (including deaths), detailing the characteristics in terms of seriousness, association with the study treatment, action taken and outcome. Details will also be given of patients' sex and age, any concomitant medication they were taking, etc.

Table 63. Individualised description of ARs and SAEs not associated with the study treatment

Patient code	Sex	Age	System organ class	Preferred term	Reported term	Start date	End date (or ongoing)	Intensity			Association with the study treatment		Action taken with the investigational medicinal product							Outcome					Concomitant medication
								1	2	3	Yes	No	1	2	3	4	5	6	7	1	2	3	4	5	

[1] Number of patients with ARs/SAEs

[2] Percentage of patients with ARs/SAEs with regard to the total number of patients available for the safety sample (n=XX)

[3] Number of ARs/SAEs

Intensity: 1. Mild / 2. Moderate / 3. Serious; **Serious:** 1. Yes / 2. No; **Association with the investigational medicinal product:** 1. Probable / 2. Possible / 3. No association; **Action taken with the investigational medicinal product:** 1. Continue / 2. Reduce / 3. Discontinue / 4. Increase / 5. Complete in accordance with the protocol / 6. Discontinue and reintroduce / 7. Not applicable; **Outcome:** 1. Recovered / 2. Not yet recovered / 3. Sequelae / 4. Fatal / 5. Unknown

Note: The fields shown in the table above are a proposal and may vary from those shown in the final report, depending on the data available once patients have been recruited.