Boehringer Ingelheim Pharma GmbH & Co. KG	Boehringer Ingelheim

Observational plan Non-interventional study	Boehringer Ingelheim Pharma GmbH & Co. KG

BI No.:	1160.218
Product:	Pradaxa® (dabigatran etexilate)
Title:	Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)
Clinical monitor:	
Scientific co-ordinator:	
Date of observational plan:	Final version: 04.06.2014 Version 1.0
Scheduled time frame of the NIS:	FPI September 2014 LPO April 2016
Confidential	

Signature page 1

SCIENTIFIC CO-ORDINATOR

Study title:

Drug persistence/adherence in patients being treated with Pradaxa®
(dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention
in non-valvular atrial fibrillation (AF)

Study number: 1160.218

I hereby declare that I will observe the requirements of the observational plan, including all the attachments.

Name:

Date: _____

Signature: _____

Signature page 2

LOCAL SIGNATURES

Study title:

Drug persistence/adherence in patients being treated with Pradaxa®
(dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention
in non-valvular atrial fibrillation (AF)

Study number: 1160.218

Trial Clinical Monitor
Date: _____

_____

Trial Statistician
Date: _____

Global Biometrics and Clinical Applications / BDM (BCA)

_____

Observational plan – Synopsis

BI OPU	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Trial clinical monitor	
BI study number	**1160.218**
Study title	Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)
Study objectives	Primary study objective: • To compare persistence in patients being treated with dabigatran etexilate or VKA. Other study objectives: • To compare adherence in patients being treated with dabigatran etexilate or VKA • To record the reasons for permanent treatment discontinuation
Target group (sites)	1000: about 670 community-based primary care internists or general practitioners and 330 cardiologists
	• Open, prospective, observational study (PMS study) in accordance with section 4(23) and section 67(6) AMG: all enrolled AF patients will be observed over 12 months during treatment with dabigatran etexilate or VKA. • In this NIS, information about dabigatran etexilate/VKA persistence and adherence will be collected in 4000 AF patients. **Visit 1 (start of observation)** • Patient data: sociodemographic data (sex, age, height, weight, education, marital status, health insurance status) • Case history of non-valvular atrial fibrillation (AF): disease onset, data on disease severity (individual components of the CHA_2DS_2-VASc score) and bleeding risk (individual components of the HAS-BLED score) • Start of treatment with dabigatran etexilate (110 or 150 mg hard capsules) or VKA (start date) • Concomitant medication: antiarrhythmics, antihypertensives, lipid-lowering agents, other prescription-only medicines

	• Number of other prescription-only medicines and frequency of daily administration (other than dabigatran etexilate/VKA)
	• Other relevant comorbidities
	Visit 2 (after about 3 months of use of dabigatran etexilate or VKA)
	• Recording of continuation of treatment with dabigatran etexilate (including dosage) or VKA since visit 1
	• Onset of adverse events since visit 1
	• Discontinuation (stop date) of treatment with dabigatran etexilate or VKA since visit 1
	  • Reasons for discontinuation of treatment with dabigatran etexilate or VKA
	  • Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
	  • In the event of treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy.
	Visit 3 (after about 6 months of use of dabigatran etexilate or VKA)
	• Recording of continuation of treatment with dabigatran etexilate (including dosage) or VKA since visit 2
	• Onset of adverse events since visit 2
	• Discontinuation of treatment (stop date) with dabigatran etexilate or VKA since visit 2
	  • Reasons for discontinuation of treatment with dabigatran etexilate or VKA
	  • Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
	  • In the event of treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy.
	• Regular use of dabigatran etexilate or VKA by means of the Morisky score
	• Number of prescription-only medicines and frequency of daily administration
	• Recording of disease severity (CHA_2DS_2-VASc score) and bleeding risk (HAS-BLED score)
	• Other relevant comorbidities
	Visit 4 (after about 9 months of use of dabigatran etexilate or VKA)
	• Recording of continuation of treatment with dabigatran etexilate (including dosage) or VKA since visit 3
	• Onset of adverse events since visit 3
	• Discontinuation of treatment (stop date) with dabigatran

	etexilate or VKA since visit 3 • Reasons for discontinuation of treatment with dabigatran etexilate or VKA • Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA • In the event of treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy. **End of observation/Visit 5 (after about 12 months of use of dabigatran etexilate or VKA)** • Recording of continuation of treatment with dabigatran etexilate or VKA since visit 4 • Onset of adverse events since visit 4 • Discontinuation of treatment (stop date) with dabigatran etexilate or VKA since visit 4 • Reasons for discontinuation of treatment with dabigatran etexilate or VKA • Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA • In the event of treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy. • Number of prescription-only medicines and frequency of daily administration • Recording of disease severity (CHA_2DS_2-VASc score) and bleeding risk (HAS-BLED score) • Other relevant comorbidities
Number of patients:	4000; 2000 on dabigatran etexilate; 2000 on VKA
Control group?	yes (x) no ()
Duration of observation / number of visits	About 12 months per patient 5 visits (inclusion visit and after about 3, 6, 9, 12 months)
Main inclusion/ exclusion criteria	Inclusion criteria: • Newly prescribed treatment with Pradaxa® (dabigatran etexilate)/VKA in the indication "Stroke prevention in non-valvular atrial fibrillation" (AF) respecting the indication and contraindications as described in the respective Summary of Product Characteristics for Pradaxa® 110 mg or 150 mg hard capsules or the appropriate VKA (patients are eligible for both Pradaxa® and VKA therapy).

	• Treatment with dabigatran etexilate or VKA is given in accordance with the respective Summaries of Product Characteristics. The routine diagnostic procedures and treatment that would be undertaken irrespective of the study are unaffected. • Only patients who are eligible *both* for therapy with Pradaxa® *and* for therapy with VKA in accordance with the respective Summaries of Product Characteristics will be documented (patients eligible for VKA *and* Pradaxa®) • Patients must have signed the patient consent form prior to inclusion in the NIS. Exclusion criteria: • Patients with the general and special contraindications mentioned in the packaging leaflet or Summary of Product Characteristics must not be included. • Patients participating at the same time or within the last 30 days in another NIS or an interventional clinical trial must not be included. • Patients treated with anticoagulants for a condition other than non-valvular atrial fibrillation must not be included. • Pradaxa® and VKA should not be used during pregnancy and lactation. Pregnant or breastfeeding women must therefore not be included in the NIS.
Target parameters	Primary endpoint: • Proportion of patients still being treated at the time of the 12-month visit with the initially allocated anticoagulant, defined as Kaplan Meier estimate at 12 months for persistence, stratified for dabigatran etexilate and VKA. Persistence is defined as the time between initiation and permanent termination of therapy. The start of treatment (documented in the CRF of visit 1) is documented as the start date and the date of discontinuation of treatment with Pradaxa® or VKA as the time of permanent termination of therapy. **Secondary endpoints:** • Proportion of patients with low, medium or high adherence at the time of the 6-month visit, stratified for dabigatran etexilate and VKA; categorisation is done on the basis of the Morisky questionnaire. • Reasons for permanent treatment discontinuation.
Safety parameters	During this NIS, all emergent adverse events (AE) will be recorded

	in the eCRF over a period of about 12 months. In the event of premature treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy.
Monitoring: source data verification?	yes (x) no ( ) 10% SDV
Drug dispensing	Prescription in accordance with the Summary of Product Characteristics
Ethics Committee approval?	yes (x)
Informed consent required?	yes (x) no ( )
Scheduled study duration	Initiation (FPI): September 2014 Last patient out (LPO): April 2016
Report	Report available: July 2016

Flowchart

Investigations / measure	Visit 1 (first examination)	Visit 2 (after about 3 months)	Visit 3 (after about 6 months)	Visit 4 (after about 9 months)	Visit 5 (after about 12 months)
Sociodemographic data	X				
AF history	X				
CHA_2DS_2-VASc -/ HAS-BLED score	X		X		X
Other relevant comorbidities	X		X		X
Recording of the start date of therapy with dabigatran etexilate (including dosage) or VKA	X				
Concomitant medication including frequency of administration	X		X		X
Recording of continuation of initial oral anticoagulation (dabigatran etexilate including dosage or VKA)		X	X	X	X
Regular use of dabigatran etexilate or VKA (Morisky score)			X		
Date of discontinuation of treatment with dabigatran etexilate or VKA, including reasons for discontinuation		X	X	X	X
In the event of discontinuation of the initial anticoagulation: antithrombotic therapy after discontinuation		X	X	X	X
Adverse events*		X	X	X	X

* In the event of premature treatment discontinuation, all emergent adverse events (AE) will be recorded in the eCRF up to 30 days after the end of therapy.

Contents

List of abbreviations

AF	Atrial Fibrillation
AMG	German Medicines Act *[Arzneimittelgesetz]*
BfArM	Federal Institute for Drugs and Medical Devices *[Bundesinstitut für Arzneimittel und Medizinprodukte]*
BI	Boehringer Ingelheim Pharma GmbH & Co. KG
CHA_2DS_2-VASc score	**C**ongestive heart failure, **H**ypertension, **A**ge (> 75), **D**iabetes mellitus, **S**troke/TIA, **V**ascular disease, **A**ge 65-74, **S**ex **c**ategory
Cmax	Maximum Concentration
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
eCRF	electronic Case Report Form
ECG	Electrocardiogram
FPI	First Patient In
HAS-BLED	**H**ypertension, **A**bnormal renal and liver function, **S**troke (1 point), **B**leeding history or predisposition, **L**abile INR, **E**lderly (>65 years), **D**rugs and Alcohol
INR	International Normalised Ratio
LÄK	State Medical Association *[Landesärztekammer]*
LPO	Last Patient Out
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
mg	Milligram
Min	Minimum
N	Number
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIS	Non-Interventional Study
OAC	Oral Anticoagulants
OPU	Operating Unit
pdf	Portable Document Format

pH	Latin: potentia hydrogenii *(power of hydrogen)*
PMS	Postmarketing Surveillance
PS	Propensity Score
PV	Pharmacovigilance
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
VFA	German Association of Research-Based Pharmaceutical Companies *[Verband forschender Arzneimittelhersteller]*
VKA	Vitamin K Antagonists
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

1.1 Medical background

Atrial fibrillation (AF) is a cardiac rhythm disorder that can occur episodically or persistently. During AF, unco-ordinated electromechanical activity of the cardiac atria occurs, triggered by rapidly succeeding, disorderly impulses that can in some cases be transmitted to the cardiac ventricles. AF is the most common cardiac arrhythmia and is associated with considerable morbidity and mortality, due in particular to a 4- to 5-fold increase in the risk of thromboembolic strokes ([1]).

Due to the high thromboembolic risk in atrial fibrillation, it is a fundamental aim of treatment to reduce the secondary complications associated with atrial fibrillation and in particular the risk of stroke. Oral anticoagulation is usually recommended for this purpose ([1];[2]). In Germany, phenprocoumon is most frequently used for anticoagulation with a vitamin K antagonist (VKA) ([3]).

In order to maintain the level of therapeutic anticoagulation within an optimum target range during treatment with VKA, the coagulation capacity of the blood must be closely monitored (i.e. at least every 3 – 4 weeks) by means of the INR value ([4]). This usually requires a visit to a physician, who can take a blood sample and perform the analysis (where necessary also via an external laboratory) and any dosage adjustment necessary.

The use of VKA is associated with various measures that can make it more difficult to use these drugs correctly. The narrow therapeutic window of VKA requires routine laboratory monitoring of coagulation (INR 2-3). However, optimal INR adjustment is often not obtained in everyday patient care in Germany either. The interactions of VKA with a number of medicines and foodstuffs require close monitoring and dosage adjustments following a change of concomitant medication or dietary habits. A recent analysis of German health insurance data came to the conclusion that AF patients with a moderate stroke risk and without any observable contraindication to OACs received no OAC on up to half the patient days observed ([5]).

1.2 Substance profile

Dabigatran etexilate is a synthetic, small-molecule, orally administered, direct inhibitor of the coagulation factor thrombin (an endogenous substance involved in the formation of blood clots, also known as factor II of the coagulation cascade). It is a medicinal product that reduces the risk of developing an obstruction of blood vessels in the brain or body (stroke or systemic embolism) as a result of the formation of blood clots in adult patients with certain heart rhythm disorders (atrial fibrillation; AF) and additional risk factors.

The prodrug dabigatran etexilate itself exhibits no pharmacological activity and is only bioactivated in vivo. Following oral administration, the compound is absorbed and hydrolysed by means of catalytic esterases in the liver and plasma to dabigatran. As a competitive, reversible direct inhibitor, dabigatran inhibits the serine protease thrombin in plasma. As thrombin causes the conversion of fibrinogen to fibrin in the coagulation cascade, its inhibition consequently prevents the development of a thrombus. In addition, dabigatran inhibits free and fibrin-bound thrombin and thrombin-induced platelet aggregation ([6]).

Dabigatran etexilate is available in hard capsules. The capsules contain pellets coated with dabigatran etexilate with a core of tartaric acid. This produces an acidic medium locally that allows absorption of the medicinal product relatively independently of variations in the pH of the gastric juice ([6]).

The absolute bioavailability of dabigatran etexilate after oral administration is approximately 6.5%. Food does not affect the bioavailability of dabigatran etexilate but does delay the time to peak plasma concentration (C_{max}) by about 2 hours ([7]).

Following oral administration of dabigatran etexilate to healthy subjects, the peak plasma concentration is reached within 2 hours in the fasting state ([6]). After repeated doses, a terminal half-life of about 12 – 14 hours has been measured ([7]).

VKA inhibit the hepatic synthesis of active coagulation factors (II, VII, IX and X) and protein C and S from inactive precursors (precursor proteins). Activation of the precursor proteins by gamma-carboxylation requires vitamin K. The regeneration of biologically active vitamin K is inhibited by VKA. In addition, further vitamin K-dependent carboxylation reactions in other organs are inhibited by VKA (e.g. in bones, kidney, placenta) ([8]; [9]).

Dabigatran etexilate differs from VKA in that it does not intervene in the hepatic synthesis of coagulation factors, but indirectly competitively inhibits a specific plasma factor. Routine monitoring in the form of coagulation tests is required during therapy with VKA, as opposed to with the use of dabigatran etexilate, because the therapeutic margin of VKA is small and the anticoagulant effect can be affected by many interactions with other medicinal products, but also with certain foodstuffs ([9],[10]).

The pharmacodynamic effect of dabigatran sets in rapidly and also declines rapidly and therefore is easily controllable and predictable. That is an essential difference from the VKA, which only become effective after a few days if the concentration of vitamin K-dependent coagulation factors has declined sufficiently and only become ineffective after a few days if there is once again sufficient production of these factors in the liver.

2 Rationale, objectives and risk-benefit analysis

2.1 Rationale for conducting the study

As well as the challenges described above, treatment compliance (persistence and adherence) represents a significant factor affecting the success of treatment ([11]).

Persistence is defined as the time between initiation and termination of therapy ([12]). Adherence describes whether patients take their medicine as prescribed. It comprises the initiation, implementation and termination of therapy ([13]). This compliance can be determined on the basis of the Morisky questionnaire. This consists of questions relating to intake behaviour ([14]). The questionnaire and its further developed version have already been used for assessing adherence during warfarin therapy, where it exhibited good validity ([15, 16]).

There are a variety of reasons for poor treatment compliance. These include patient-related aspects (e.g. socioeconomic status, personal convictions), but also disease-related (e.g. symptom severity) and medication-related (e.g. frequency of intake, side effects) aspects ([17]). This also applies particularly to patients with AF who require permanent oral anticoagulation ([18]). In terms of anticoagulation for the prevention of strokes, one important aspect is the fact that in the patients' subjective view it does not improve their condition and only the absence of a negative event (e.g. stroke) motivates them to continue treatment. This could limit treatment compliance and reduce the acceptance of side effects.

In addition, it has not yet been elucidated whether omission of the routine monitoring of coagulation status during treatment with dabigatran etexilate and the associated feedback to patients has any effect on treatment adherence in everyday therapeutic use. An analysis of Canadian health insurance data shows that drug persistence following the initiation of everyday care is higher during treatment with dabigatran etexilate than during VKA therapy ([19]).

No studies have yet been undertaken as to whether there are differences in persistence and adherence within the German care context between patients treated with Pradaxa® or VKA. For this reason, a contribution to the resolution of this question constitutes a relevant gain in knowledge.

2.2 Study objectives

The objective of this open, prospective, controlled, multicentre, non-interventional cohort study (NIS) is to record the treatment compliance (measured as persistence and adherence) of patients treated with dabigatran etexilate or VKA.

Primary study objective:

- To compare persistence in patients treated with dabigatran etexilate or VKA.

Secondary study objectives:

- To compare adherence in patients treated with dabigatran etexilate or VKA
- To record the reasons for any treatment discontinuation

2.3 Risk-benefit analysis

Treatment will be administered in accordance with the marketing authorisation of dabigatran etexilate or VKA for AF patients requiring permanent oral anticoagulation.

The medicinal products Pradaxa® or VKA used in this NIS are authorised in the Federal Republic of Germany.

The medicines under observation are not provided by the marketing authorisation holder but are prescribed by the participating physician in accordance with the indication.

The choice of treatment is at the sole discretion of the participating physicians. The NIS has no effect on the patient's treatment. The decision to include a patient in an NIS is distinct from the decision to prescribe the medicinal product.

No additional medical procedures are required other than those which the patient would have received even if they were not included in the NIS. The treatment, including diagnosis and monitoring, follows the standard medical treatment practice.

There is therefore no risk to patients over and above the usual treatment risk for AF patients on anticoagulant therapy with dabigatran etexilate or VKA even outside the NIS.

3 Description of study design and patient population

3.1 General remarks on the study design and plan

This is an open, prospective, non-interventional study (NIS) in accordance with sections 4.23 and 67.6 of the AMG.

The NIS is being conducted by Boehringer Ingelheim Pharma GmbH & Co. KG. The scientific co-ordinator i

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Any changes in the study management in the course of the study will be notified in writing to the observing physicians where necessary.

3.1.1 Administrative structure of the NIS

About 10,000 potential sites spread over the whole of Germany (general practitioner and primary care internist practices as well as cardiology practices) will be reviewed by members of the Boehringer Ingelheim Pharma GmbH & Co. KG pharmaceutical sales force for their eligibility for participation in the study.

About 3000 sites interested in participating and able to document four patients treated with either dabigatran etexilate or VKA within a period of six months can be selected by Boehringer Ingelheim for possible participation. The 1200 sites that actually participate are chosen by randomisation. It will be assumed that, following the recruitment of about 1200 sites, 1000 sites will actually actively document patients.

Of the 1000 active sites, approximately 2/3 (about 670) will be community-based primary care internists/general practitioners and approximately 1/3 (about 330) community-based cardiologists across Germany.

As a result of the random selection of participants, a high degree of representativeness of the collected data can be obtained and a selection bias in the choice of participating practices can be avoided.

All sites and their employees involved in study participation will be trained before the start of the study in its content and the documentation process.

Following initiation, each doctor should document alternately the first successive eligible patients for whom he has decided to prescribe therapy with dabigatran etexilate or VKA.

The rights and duties of the participating doctors and Boehringer Ingelheim Pharma GmbH & Co. KG derive from the contract concluded on the conduct of an NIS. The participating physicians undertake to conduct the NIS responsibly in accordance with the agreements made in the contract.

Boehringer Ingelheim Pharma GmbH & Co. KG will pay participating physicians compensation in accordance with the listing in the contract concluded with them.

3.2 Discussion of study design

The intention of this NIS is to collect data on the persistence and adherence to anticoagulant therapy of AF patients with dabigatran etexilate or VKA in daily practice.

An NIS appears the most suitable instrument for obtaining information about the use of medicines in everyday therapeutic practice and thus for investigating prospectively unresolved questions in everyday therapeutic practice as independently as possible.

A sample of 4000 patients offers the opportunity to document and assess the persistence and adherence to anticoagulant therapy of AF patients during therapy with dabigatran etexilate or VKA in a representative patient population.

3.3 Choice of patient population

The treatment decision is made independently of participation in this NIS and is taken before participation is considered.

A list of patients who have given their consent to participate in the NIS will be kept for each site. This list will be stored confidentially in the study folder.

3.3.1 Main diagnosis

Four thousand patients with non-valvular atrial fibrillation, in whom anticoagulant treatment with Pradaxa® or VKA is indicated in accordance with the guidelines and in line with the Summary of Product Characteristics, must be observed in about 1000 practices (community-based cardiologists and primary care internists / general practitioners) in this NIS.

Before the start of therapy with Pradaxa® or VKA, due note must be taken of the contraindications. See also the respective current Summaries of Product Characteristics of Pradaxa® or the VKA used.

Patients treated with VKA must also theoretically be treatable with dabigatran etexilate to ensure comparability of the patient populations.

3.3.2 Inclusion criteria:

Patients can be included if all the following criteria are present:

- Newly prescribed treatment with Pradaxa® (dabigatran etexilate)/VKA in the indication “Stroke prevention in non-valvular atrial fibrillation” (AF) respecting the indication and contraindications as described in the respective Summary of Product

Characteristics Pradaxa®110 mg or 150 mg hard capsules or the appropriate VKA (patients are eligible for both Pradaxa® and VKA therapy).

- Only patients who are eligible *both* for therapy with Pradaxa® *and* for therapy with VKA in accordance with the respective Summaries of Product Characteristics are documented (patients eligible for VKA *and* Pradaxa®)
- Treatment with dabigatran etexilate or VKA is given in accordance with the respective Summaries of Product Characteristics. The routine diagnostic procedures and treatment that would be undertaken irrespective of the study are unaffected.
- Only patients on VKA therapy who would also be eligible for therapy with dabigatran etexilate in accordance with the Pradaxa® Summary of Product Characteristics are documented.
- Patients must have signed the patient consent form before inclusion in the NIS.

3.3.3 Exclusion criteria

- Patients with the general and special contraindications mentioned in the packaging leaflet or Summary of Product Characteristics must not be included.

  The Summaries of Product Characteristics for Pradaxa® are contained in the NIS study folder in the register "Summaries of Product Characteristics".

  For the selected VKA, the observing physician must use the current Summary of Product Characteristics of the product concerned for guidance.
- Patients participating at the same time or within the last 30 days in another NIS or an interventional clinical trial must not be included.
- Patients treated with anticoagulants for a condition other than non-valvular atrial fibrillation must not be included.
- Pradaxa® and VKA should not be used during pregnancy and lactation. Pregnant or breastfeeding women must therefore not be included in the NIS.

3.3.4 Exclusion of patients from the NIS

3.3.4.1 Exclusion of individual patients from the NIS

The individual patient has the right to withdraw their consent to participate in the NIS at any time. Discontinuation of participation in the NIS by the patient has no effect on the patient's routine treatment.

3.3.4.2 Termination of the NIS by the sponsor

Following the onset of one or all of the following events, the study can be terminated at the sponsor's discretion:

- Presence of medical or ethical reasons impacting on the continuation of the study in the patients' interests
- Recruitment problems

4 Treatment

4.1 Administered medications

4.1.1 Products

Treatment-naive AF patients will be treated with Pradaxa® hard capsules or VKA in accordance with the Summary of Product Characteristics:

Direct oral thrombin inhibitor:	Pradaxa® 150 mg hard capsules Pradaxa® 110 mg hard capsules
Vitamin K antagonists	e.g. phenprocoumon

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

The choice of VKA is at the discretion of the observing physician. There is no set dosage for these products.

The Summaries of Product Characteristics for Pradaxa® are contained in the NIS study folder in the register "Summaries of Product Characteristics".

For the selected VKA, the observing physician must use the current Summary of Product Characteristics of the product concerned for guidance (www.fachinfo.de).

4.1.2 Allocation of patients and treatment

Each physician must include the first 4 successive eligible AF patients to whom he has decided to prescribe anticoagulant therapy with either dabigatran etexilate or VKA.

Inclusions must be alternated in a ratio of 1 patient on dabigatran etexilate to 1 patient on VKA so as to ensure equal treatment group sizes. The consecutive inclusion of the first 4 eligible AF patients is intended to prevent a selection bias in the choice of patients.
To allow comparability of the patients between the cohorts, matched pairs of dabigatran etexilate and VKA patients are formed for the analysis.

The decision to treat is made irrespective of participation in this NIS and is taken before any consideration of participation.

4.1.3 Dosage

Treatment with dabigatran etexilate or VKA must be given in accordance with the data in the respective Summary of Product Characteristics and is based solely on medical therapeutic needs.

Pradaxa®

The recommended daily dose of Pradaxa® is 300 mg, taken in the form of one 150 mg capsule twice daily. Treatment should be long term.

For the following two patient groups, the recommended daily dose of Pradaxa® is 220 mg, taken as one 110 mg capsule twice daily:

- Patients ≥ 80 years

- Patients receiving verapamil concomitantly.

For the following groups, a daily dose of 300 mg or 220 mg of Pradaxa® will be chosen on the basis of an individual assessment of the thromboembolic risk and the bleeding risk:

- Patients between 75 and 80 years old
- Patients with moderate renal impairment
- Patients with gastritis, oesophagitis or gastroesophageal reflux
- Other patients with an increased bleeding risk.

Note: The recommended doses in the Summary of Product Characteristics must not be exceeded.

VKA

VKA have no set dosage.

The dosage of VKA (e.g. phenprocoumon) must be monitored by determining the thromboplastin time and adapted individually. The outcome of this determination is given as INR (International Normalised Ratio).

The target is an effective range of 2.0–3.0 INR.

4.1.4 Other

The medication is supplied on prescription. Patients receive their medicines in the pharmacy. These are commercially available products.

The storage conditions described on the pack apply.

A pill count is not undertaken in connection with the NIS as this cannot be expected in routine care.

4.2 Concomitant medication and restrictions

Patients can receive any medicines they would also receive in their usual routine treatment.

Patients who have the general and special contraindications mentioned in the respective package leaflets or Summaries of Product Characteristics must not be included.

Patients participating at the same time or in the last 30 days in another NIS or interventional clinical trial must not be included.

5 Investigations and observation parameters

Data collection must always be done prospectively.

No data on efficacy in the conventional sense are collected. In this NIS, data on the persistence and adherence to anticoagulant therapy with dabigatran etexilate or VKA will be recorded as target parameters.

5.1 Target parameters

5.1.1 Primary and secondary endpoints

Primary endpoint:

- Proportion of patients still being treated at the time of the 12-month visit with the initially allocated anticoagulant, defined as Kaplan Meier estimate at 12 months for persistence, stratified for dabigatran etexilate and VKA. Persistence is defined as the time between initiation and permanent termination of therapy ([20]). The start of treatment (documented in the CRF of visit 1) is documented as the start date and the date of discontinuation of treatment with Pradaxa® or VKA as the time of permanent termination of therapy

Secondary endpoints:

- Proportion of patients with low, medium or high adherence at the time of the 6-month visit, stratified for dabigatran etexilate and VKA; categorisation is done on the basis of the Morisky questionnaire.
- Reasons for permanent treatment discontinuation.

5.1.2 Investigation of target parameters

Following information and consenting of the patients, patient data relating to their sociodemographic factors, AF disease history, initial anticoagulant treatment and prior and concomitant medication will be recorded as part of this NIS.

AF patients will use Pradaxa® or VKA in accordance with the respective Summaries of Product Characteristics.

The continuation of treatment with Pradaxa® or VKA and any reasons for discontinuation will be recorded approximately quarterly over the observation period of 12 months (after about 3, 6, 9 and 12 months).

After about 6 months of observation, in addition to the continuation of therapy with Pradaxa® or VKA, drug adherence will be investigated and documented by means of the Morisky questionnaire and the continuation of antithrombotic treatment recorded at a regular follow-up visit.

After about 12 months of observation, in addition to the continuation or discontinuation of treatment with Pradaxa® or VKA, the continuation of antithrombotic treatment will be recorded at a regular follow-up visit.

All patient data will be recorded in pseudonymised form and documented in the eCRF.

5.2 Safety parameters

5.2.1 Safety endpoints

In the context of this NIS, all emergent adverse events (S/AE) will be recorded approximately quarterly for 12 months in the eCRF.

In the event of treatment discontinuation, all emergent adverse events (S/AE) will be recorded in the eCRF up to 30 days after the end of treatment.

In the event of discontinuation of oral anticoagulation, the reasons for discontinuation and the subsequent antithrombotic stroke prophylaxis will be recorded.

5.2.2 Investigation of adverse events

5.2.2.1 Definition of adverse events

Adverse event:

Adverse events (AE) are all harmful, pathological or unintended changes of anatomical, physiological or metabolic functions, identifiable by physical signs, symptoms and/or changes in laboratory values that occur during the course of the NIS, irrespective of whether or not a relationship with a medication is assumed.

Regardless of whether a causal relationship exists with the consumption of the medication, adverse events include:

- all complaints by patients of a lack of well-being or subjective and objective symptoms (including clinically relevant changes in laboratory findings)
- new diseases and accidents observed during treatment with the medication
- the exacerbation of an existing disease
- the lack of efficacy of a medicinal product
- resistance formation
- abuse
- misuse
- overdose
- habituation, dependence
- off-label use
- interactions

Serious adverse event:

An adverse event is serious (SAE) if it

- results in death,
- is immediately life-threatening,
- results in permanent or significant disability/incapacity,
- requires or prolongs hospital treatment,
- involves congenital malformations or a birth defect,
- is otherwise medically significant.

Severity of an adverse event

The severity of adverse events must be documented in the (e)CRF and classified in accordance with the current version of the NCI-CTCAE criteria.

Causal relationship with an adverse event

The causal relationship must be medically assessed and evaluated and include all relevant factors, including the response pattern, time course, outcome after discontinuation of the trial medication or re-exposure, other confounding factors such as concomitant medication, concurrent diseases and relevant past history. The assessment of the causal relationship must be documented in the (e)CRF as follows:

Yes = There is a plausible causal relationship between the administered medication and the adverse event

No = There is no plausible causal relationship between the administered medication and the adverse event

Exacerbation of pre-existing diseases and other pre-existing conditions

The exacerbation of pre-existing diseases and other pre-existing conditions is documented as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination results and laboratory values

Changes in vital signs, ECG, physical examination results and laboratory values are documented as (S)AE in the (e)CRF if they are classed as clinically relevant by the observing physician.

5.2.2.2 Report of (serious) adverse events

All adverse events (SAE and AE) that occur in the course of this NIS (in other words between the signature of the informed consent form and the end of the observation phase after about 12 months or up to 30 days after the end of treatment in the event of premature treatment discontinuation) will be collected regardless of whether the trial medication was taken or regardless of whether or not there is a causal relationship between trial medication and (S)AE.

SAEs and AEs associated with SAEs must be documented in the (e)CRF within 24 hours of becoming known so as to be reported promptly to Boehringer Ingelheim Pharmacovigilance (see 5.4).

All other AEs must be documented in the (e)CRF within 14 days of becoming known.

Following documentation in the (e)CRF, they are **automatically** reported to Boehringer Ingelheim Pharmacovigilance within 24 hours in the form of a pdf file. The BI SAE/AE form is generated from the eCRF at the same time.

If there is no internet access at the time of the report, alternatively a fax must be sent to the following address:

Boehringer Ingelheim Pharma GmbH & Co.KG
Pharmacovigilance Germany (PV Germany)
Binger Straße 173
55216 Ingelheim
Fax: +49 (6132) 72 - 141522
Email: PV_local_Germany@boehringer-ingelheim.com

For each (S)AE, the start and end date, severity, any treatment required, outcome of the event, severity of the event (serious/non-serious) and any measures in relation to the medication being studied must be noted.

The observing physician indicates the causal relationship with the medication being studied for all (S)AEs, as defined in section 5.2.2.1.

In the event of a premature treatment discontinuation, the observing physician must also report (S)AEs that occur up to 30 days after the end of treatment. Each (S)AE reported to Boehringer Ingelheim during this period must be documented in the safety database.

If new information should be obtained after the initial report of the adverse event, this must also be reported in line with the previously mentioned procedure.

The above-mentioned duty of notification to Boehringer Ingelheim extends also to documented reports on uses of a Boehringer Ingelheim medicinal product during pregnancy, irrespective of whether or not an adverse event has occurred.

Pregnancy notifications must be documented on the appropriate forms and faxed to the following address:

Boehringer Ingelheim Pharma GmbH & Co.KG
Pharmacovigilance Germany (PV Germany)
Binger Straße 173
55216 Ingelheim
Fax: +49 (6132) 72 - 141522
Email: PV_local_Germany@boehringer-ingelheim.com

5.3 Appropriateness of investigations

Determination of persistence by quarterly recording of the continuation of treatment as a parameter for the treatment administered or discontinued. Adherence is recorded using the Morisky questionnaire. The Morisky questionnaire relates to intake behaviour. The questionnaire has already been used to assess adherence to warfarin therapy, where it exhibited good validity ([16]).

6 Observational plan

The arrangement of separate visits to the doctor is not necessary for the NIS.

The Boehringer Ingelheim (BI) GP practice sales force will present the NIS to about 3000 eligible practices.

Following random selection, about 12,000 eligible doctors will sign a contract on participation in the NIS.

Following the decision to use treatment with dabigatran etexilate or VKA in an AF patient and before the prescription of treatment with dabigatran etexilate or VKA, the doctor will consider whether the patient is eligible for participation in the NIS. If he recommends treatment with dabigatran etexilate or VKA to the patient, he can then also propose participation in the NIS.
The doctor will explain the nature of the study to the patient and obtain their written consent to the processing of patient data for the purpose of this NIS and source data verification. Where possible, 4 successive eligible patients will be included in the NIS in a ratio of 1:1 (1 dabigatran etexilate : 1 VKA, alternately).

6.1 Timetable of visits

Following information and consenting, patient data on sociodemographic factors, previous history including risk of stroke and bleeding and the patients' prior and concomitant medication will be recorded at visit 1 as part of this NIS.

AF patients will use Pradaxa® or VKA in accordance with the respective Summaries of Product Characteristics.

Treatment with Pradaxa® or VKA will be recorded approximately quarterly over the observation period of 12 months (at a regular visit after about 3, 6, 9 and 12 months).

In addition, any emergent adverse events will be documented at these visits and discontinuation and any reasons for discontinuation recorded.

Reasons for discontinuation include intolerable adverse events, intolerability or insufficient efficacy of treatment with dabigatran etexilate or VKA.

After about 6 months of observation, in addition to the continuation of therapy, treatment adherence will be investigated and documented by means of the Morisky questionnaire at a regular follow-up visit.

The patient has the right to end their participation in the NIS at any time without giving a reason.

6.2 Details of visits

Visit 1 (start of observation)

- Patient data: sociodemographic data (sex, age, height, weight, education, marital status, health insurance status)
- Case history of non-valvular atrial fibrillation (AF): disease onset, data on disease severity (individual components of the CHA_2DS_2-VASc score) and bleeding risk (individual components of the HAS-BLED score)
- Start of treatment with dabigatran etexilate (110 or 150 mg hard capsules) or VKA (start date)
- Concomitant medication: antiarrhythmics, antihypertensives, lipid-lowering agents, other prescription-only medicines
- Number of other prescription-only and frequency of daily administration (other than dabigatran etexilate/VKA)
- Recording of relevant comorbidities (Charlson et al. 1987)[21]

Visit 2 (after about 3 months of use of dabigatran etexilate or VKA)

- Recording of the continuation of therapy with dabigatran etexilate (including dosage) or VKA since visit 1
- Onset of adverse events since visit 1
- Discontinuation of treatment with dabigatran etexilate or VKA since visit 1
    - Reasons for the discontinuation of treatment with dabigatran etexilate or VKA
    - Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
    - In the event of treatment discontinuation, all emergent adverse events (AE) are recorded in the eCRF up to 30 days after the end of therapy.

Visit 3 (after about 6 months of use of dabigatran etexilate or VKA)

- Recording of the continuation of therapy with dabigatran etexilate (including dosage) or VKA since visit 2
- Onset of adverse events since visit 2
- Discontinuation of treatment with dabigatran etexilate or VKA since visit 2
  - Reasons for the discontinuation of treatment with dabigatran etexilate or VKA
  - Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
  - In the event of treatment discontinuation, all emergent adverse events (AE) are recorded in the eCRF up to 30 days after the end of therapy.
- Regular use of dabigatran etexilate or VKA by means of the Morisky score
- Number of prescription-only medicines and frequency of daily administration
- Recording of disease severity (individual components of the CHA_2DS_2-VASc score) and bleeding risk (individual components of the HAS-BLED score)
- Recording of relevant comorbidities (Charlson et al. 1987)[21]

Visit 4 (after about 9 months of use of dabigatran etexilate or VKA)

- Recording of the continuation of therapy with dabigatran etexilate (including dosage) or VKA since visit 3
- Onset of adverse events since visit 3
- Discontinuation of treatment with dabigatran etexilate or VKA since visit 3
  - Reasons for the discontinuation of treatment with dabigatran etexilate or VKA
  - Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
  - In the event of treatment discontinuation, all emergent adverse events (AE) are recorded in the eCRF up to 30 days after the end of therapy.

End of observation/Visit 5 (after about 12 months of use of dabigatran etexilate or VKA)

- Recording of the continuation of therapy with dabigatran etexilate (including dosage) or VKA since visit 4
- Onset of adverse events since visit 4
- Discontinuation of treatment with dabigatran etexilate or VKA since visit 4
  - Reasons for the discontinuation of treatment with dabigatran etexilate or VKA
  - Antithrombotic therapy after discontinuation of treatment with dabigatran etexilate or VKA
  - In the event of treatment discontinuation, all emergent adverse events (AE) are recorded in the eCRF up to 30 days after the end of therapy.
- Number of prescription-only medicines and daily intake

- Recording of disease severity (individual components of the CHA_2DS_2-VASc score) and bleeding risk (individual components of the HAS-BLED score)
- Recording of relevant comorbidities (Charlson et al. 1987)[21]

It is anticipated that anticoagulated patients will be invited for follow-up by the doctor at least quarterly. The quarterly recording of prescriptions and patient data therefore appears compatible with the real-life care situation in Germany.

7 Statistical analysis

All the analyses associated with this observational study are purely descriptive; results are to be interpreted exploratorily. There are no predefined confirmatory hypotheses and no measures are taken to maintain a study-wide 5% significance level or simultaneous confidence intervals.

7.1 Statistical design model

This is a non-randomised, open, multicentre, non-interventional cohort study with patients who are suffering from non-valvular atrial fibrillation and have recently been prescribed an oral anticoagulant (VKA or dabigatran etexilate). As the treatment is attributed by the doctor, differences in patient characteristics between the two patient groups receiving VKA or dabigatran treatment that are to be compared may be expected. To improve the comparability of the treatment groups and hence increase the internal validity, the analysis of the primary target variable (persistence) is planned using methods such as matching or trimming of the population and adjustment.

7.2 Null and alternative hypothesis

As all analyses are performed descriptively, there is no confirmatory null and alternative hypothesis formulation.

7.3 Planned analyses

The evaluation is performed using SAS® software. All analyses are descriptive. For end-of-text tables, N / mean / SD / min / median / max are given as statistical characterisation measures for constant variables; for categorial variables, N / % per category are given.
All patients documented in the CRF with at least one prescription for dabigatran etexilate or VKA and who meet the inclusion criterion (main diagnosis: non-valvular AF) are included in the analyses (i.e. “all eligible patients”). For the analysis of adverse events, all patients documented in the CRF with at least one prescription for dabigatran etexilate or VKA will be included in the analyses. In order to allow a valid comparison of compliance (persistence and adherence), a 1:1 matching of patients prescribed dabigatran or VKA will be performed based on the exposure propensity score (PS). The propensity score is calculated on the basis of a logistic regression model in which the choice of treatment is included in the model as a dependent variable and further relevant baseline characteristics are considered as independent variables in the model. The relevant baseline characteristics included in the PS model will be predefined in the analysis plan. The choice is based on the premise that all baseline variables for which a priori an association with persistence and/or adherence is expected are to be

included. These variables correspond to the potential confounder variables for a comparative analysis.

Baseline patient characteristics

The cohort resulting from the 1:1 matching as well as the whole cohort of all eligible patients will be characterised, stratified by treatment group, in terms of demographic data, concurrent diseases, concomitant medication, data on AF severity and other baseline characteristics (including risk score for stroke and bleeding, i.e. CHADS-VASc and HAS-BLED).

Persistence and reasons for treatment discontinuation

The analysis is performed on the basis of the patient cohorts resulting from the 1:1 matching. Kaplan Meier estimates for the time to discontinuation of treatment (cf. definition in section 5.1.) will be calculated separately for the dabigatran and the VKA patient group and illustrated graphically. In particular, the Kaplan Meier estimates for persistence at time 3, 6, 9 and 12 months will be reported. The comparison in terms of the persistence of patients on treatment with dabigatran versus VKA will be performed by means of the stratified log-ranked test, which takes account of the dependency of treatment groups resulting from matching (cf. Klein, Moeschberger, 1997, [22]). Patients who discontinued the study prematurely and for whom no treatment discontinuation is documented will be censured at the time of study discontinuation. Patients who end the study as planned will be censored on the day after the last visit if no previous treatment discontinuation is documented.
The absolute number and proportion of patients discontinuing the initial treatment in the course of the study will be summarised overall and according to the reasons for discontinuation for the dabigatran and VKA cohorts.

The association of patient characteristics (including treatment allocation) with persistence will be investigated by means of Cox regression models (univariate and multivariate models). Baseline characteristics will be presented stratified for patients who discontinue the treatment in the course of the study and those who do not.

A multivariable Cox regression model (including the factors used for calculating the PS and choice of treatment) will be reported as a sensitivity analysis. For this analysis, all patients who are within the common supports of the empirical density function of the PS (instead of matched pairs) will be included; the common support is determined after excluding patients with a propensity score above the 97.5% percentile and below the 2.5% percentile in each treatment group in order to avoid a strong influence from patients with extreme PS values.

Adherence

The analysis is performed on the basis of the patient cohort resulting from 1:1 matching. The Morisky questionnaire consists of 8 questions and will be presented at the time of the 6-month visit. The analysis and categorisation of patients into the categories

- poor adherence (score >2)
- medium adherence (score=1, 2) and
- high adherence (score=0)

is performed according to Morisky. For patients who have not answered one or more questions, this score is not calculated. If the proportion of patients with missing answers is high (e.g. >20%), a sensitivity analysis will be performed, in which the score will also be

calculated if up to 2 questions per patient are missing[23]. Patients who at the time of the visit are no longer on the initial therapy and those who have already discontinued the study before this time will be described separately from those for whom the Morisky score cannot be calculated for other reasons. Patients with missing values are analysed in terms of their baseline characteristics in comparison with patients with an evaluable Morisky score; patients with missing values will be stratified into the above-mentioned groups of study drop-outs, treatment drop-outs and patients with missing values for other reasons and the analysis will only be performed for strata with at least 200 patients (total and per treatment group).

The number and proportion of patients who fall into the different adherence classes will be presented for the dabigatran and VKA patients.

Coding

The current version of the Medical Dictionary for Drug Regulatory Activities will be used for coding adverse events. Concomitant medication will be coded using the current version of the WHO-DD.

Analysis of safety endpoints

For the analysis of adverse events, all patients documented in the CRF with at least one prescription for dabigatran etexilate or VKA will be included. Analyses of adverse events are descriptive and will be performed in accordance with Boehringer Ingelheim standards. In the analysis of adverse events, the focus is on treatment-emergent events. Events that occur in the period between the start of treatment and the permanent discontinuation of treatment or the end of the study (in patients in whom no permanent discontinuation of the medication is documented in the course of the study) + 6 days are categorised as treatment emergent and will be presented in frequency tables for dabigatran and VKA patients.

Adverse events that occur before or after this period will be assigned to “screening” or “post-treatment” and only presented in listings.

Frequency, severity and causal relationship of treatment-emergent adverse events will be tabulated in accordance with MedDRA System Organ Class and Preferred Term. Patients with treatment-emergent serious adverse events (SAEs) will be presented in tables. In addition, significant adverse events and adverse events resulting in treatment discontinuation will be investigated.

No interim analyses are planned.

7.4 Procedure for missing data

All available information will be used in the data analysis. Drop-outs will be duly considered in the main analysis by virtue of the methodology used (survival time analysis).

Missing values will be identified as such and no replacement is planned.

7.5 Determination of number of patients

It is planned to include a total of 4000 patients in this non-interventional, controlled, observational study (dabigatran etexilate: 2000 patients, VKA: 2000 patients).

Calculation of statistical power:
All analyses are purely exploratory by virtue of the non-interventional study design. On the following assumptions:

- 15% drop-outs /missing values after one year,
- 2000 dabigatran etexilate patients, 2000 VKA patients, with 66% of VKA patients with a matching partner in the dabigatran etexilate group
  (i.e. total number of patients in the 1:1 matched analysis is **2640**)
- a persistence rate of 63% in the dabigatran etexilate group (cf. 1-year persistence with a 60-day permissible medication gap as reported by Zalesak ([19])).

the power for a descriptive p value <=0.05 in a 2-tailed test for the same persistence rates is as follows (dependent on the VKA persistence rate):

Assumed VKA persistence rate*	**51%**	**53.8%**	**56.5%**
Power	100%	99.7%	91.7%

* The calculations were performed with ADDPLAN6 and are based on survival time analysis test statistics and the endpoint variables “Time to permanent treatment discontinuation”.

8 Declaration of consent, data protection, NIS documentation

8.1 Study approval, patient information and consent

8.1.1 Administrative requirements

This NIS will be conducted in accordance with sections 4.23 and 67.6 of the Medicines Act of the Federal Republic of Germany (AMG) and the recommendations of the Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich Institute for the planning, conduct and evaluation of postmarketing surveillance studies, as well as relevant BI standard operating procedures (SOPs).

In accordance with section 67.6 AMG, the NIS will be notified by Boehringer Ingelheim Pharma GmbH & Co. KG or the duly contracted institute to the Federal Associations for Statutory Health Insurance Physicians, National Association of Statutory Health Insurance Funds, the Association of Private Health Insurance Funds and the competent Federal supervisory authority (BfArM).

The doctors involved will also be designated by name, the nature and amount of the compensation paid to them will be reported and a copy of the agreements concluded with them will be forwarded to the Federal Associations for Statutory Health Insurance

Physicians, National Association of Statutory Health Insurance Funds and the Association of Private Health Insurance Funds.

Copies of the notifications, where these have not been made purely electronically, will be filed in the appropriate register in the investigator's folder.

In addition, provision is made for an entry in the publicly accessible clinicaltrials.gov database in accordance with the Notification of the Association of Research-Based Pharmaceutical Companies (VFA).

The NIS will be assessed by the ethics committee of the Baden-Württemberg LÄK *(State Medical Association)* before the start, and likewise any changes to the observational plan. A copy of the approval can be found in the corresponding register in the study folder.

In addition, each participating physician must be advised by his Ethics Committee in accordance with the code of professional conduct.

8.1.2 Patient information and consent

The doctor will explain the nature of the study to the patients and obtain their written consent to the processing of patient data for the purposes of this NIS and for source data verification in accordance with the current data protection guidelines.

The patient will receive one original of his or her written consent. The other original will be kept in the study folder.

It is important that this step is performed before the patient is included in the NIS and observations entered in the eCRF.

It must be documented in the eCRF that the patient's consent has been obtained before the beginning of the observation.

8.2 Data quality and assurance

This NIS is conducted in accordance with sections 4.23 and 67.6 of the Medicines Act of the Federal Republic of Germany (AMG) and the recommendations of the Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich Institute for the planning, conduct and evaluation of postmarketing surveillance studies, as well as relevant BI standard operating procedures (SOPs).

The data from the NIS mentioned under 6.2 will be recorded on internet-based electronic documentation forms (eCRF). All documentation forms in the eCRF must be completed in full.

All entries in the eCRF and the existing codings will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. The patient questionnaires are entered directly into the database via entry masks at the CRO.

To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the trial site: plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.

If corrections are necessary after the data are input, these will be documented in an audit trail.

For the further quality assurance of the documented patient observations, a sample-based source data comparison will be performed on about 10% of the sites, in the course of which the documented data will also be checked on site for completeness and consistency. An additional inspection/quality assurance check of this NIS can be performed.

8.2.1 Data protection

Before patients can be included in this NIS, they will be given an explanation of the processing of personal data and comprehensively informed about the transmission of their data to third parties concerned. They will be asked to give their written consent to this.

Patient data will be recorded in pseudonymous form. A list of patients who have given their consent to participate in the NIS will be kept for each site. This list will be kept confidentially in the study folder. Patient allocation is done on the basis of year of birth and the patient number issued at the participating trial site.

All information collected during the NIS will be treated confidentially at all times. Previous history data and data on therapeutic measures, emergent side effects and disease course will be obtained from patients in the course of this NIS.

All the recorded data will serve to answer the above-mentioned questions and will be recorded at the trial site using an electronic documentation system (eCRF) from

.

8.3 Documentation of the NIS

The Morisky questionnaire completed by the patient as part of visit 3 is sent to the attendant CRO, where it is entered in the database.

All other data from the NIS mentioned under 6.2 will be recorded in an electronic documentation system (eCRF).

8.3.1 Source data

All participating doctors are obliged to record patients' participation in the NIS in the patients' original documents.

In the event of any queries, the participating doctor must be able to identify the observed patient.

Medical information about patients may only be communicated and analysed under the patients' number.

8.3.2 Direct access to source data and documents

By signing the contract, the participating site has consented to source data verification, which will take place at the participating sites.

For quality assurance of the documented patient observations, a source data comparison is undertaken sample-based on about 10% of the sites, following which the documented data are also checked on site for completeness and consistency.

8.3.3 Archiving of documents

The observing physician will keep the original documents in accordance with the statutory retention time.

All study-specific documents will be archived by Boehringer Ingelheim Pharma GmbH & Co. KG for a period of 10 years after the end of this NIS.

8.4 Listing and accelerated reporting procedure of adverse events

As the marketing authorisation holder of Pradaxa®, Boehringer Ingelheim International GmbH is responsible for the accelerated reporting of serious adverse events, such as SUSARs, in accordance with the currently applicable statutory requirements.

8.5 Confidentiality statement

The observing physician undertakes to observe the confidentiality of all data, information, results and findings that he obtains in the course of conducting the NIS or that are disclosed to him by BI Pharma directly or indirectly ("confidential information") and to use them only in association with the conduct of the NIS.

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10 Attachments

Attachment 1: Morisky questionnaire

NIS 1160.xxx:

Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)

Site number:_____ Patient number:_____ Visit 3, date:_____

Dear patient,

You have said that you are taking medicine for stroke prevention in atrial fibrillation.

Some patients have experienced various problems associated with their medication-taking behaviour and we are interested to find out about your experiences.

There are no right or wrong answers.

Please answer each question on the basis of your personal experience with your medicine for stroke prevention in atrial fibrillation.

Please tick the answer that applies		**No**	**Yes**
1.	Do you sometimes forget to take your stroke prevention tablets?		
2.	People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine for stroke prevention?		
3.	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
4.	When you travel or leave home, do you sometimes forget to bring along your medicine for stroke prevention?		
5.	Did you take your medicines for stroke prevention yesterday?		
6.	When you feel like your stroke prevention is under control, do you sometimes stop taking your medicine?		
7.	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		

Please tick the answer that applies		**Never/rarely**	**Once in a while**	**Sometimes**	**Usually**	**All the time**
1.	How often do you have difficulty remembering to take all your medicine?					

Attachment 2: (S)AE form

Please send immediately to Boehringer Ingelheim Pharma GmbH & Co KG on Fax No. 06132-72-141522 or PV_Germany.de@boehringer-ingelheim.com. Leave shaded areas blank.

Boehringer Ingelheim

Report of Serious/Non-Serious Adverse Events in Non-Interventional Study (NIS)

NIS title: 1160.218 / Pradaxa®

Site number: |__|__|__|__|

OPU case ID number:

Pat. initials: |__|__|__|

Pat. No.: |__|__|

Reporter name / telephone and fax number

_____

_____

BI CTMS number: 1160.218

Sex	Date of birth (Day / Month / Year)	Age	Height (cm)	Weight (kg)	Race	Pregnant
1 ☐ male 2 ☐ female	|__|__| |__|__|__| |__|__|	|__|__|	|__|__|__|	|__|__|__| . |__|	1 ☐ White 2 ☐ Black 3 ☐ Asian	0 ☐ no 1 ☐ yes **Week:** |__|__|

☐ **Initial** report

☐ **Follow-up** report

Event:

Describe all observed events, symptom(s).

Also all non-serious events associated with the serious event.

Date of the event

(enter date for **each** event)

If still ongoing at the end, enter "ongoing" in the 'End date' column

Intensity of the event: 1= mild; 2= moderate; 3= severe

Therapy of the event: 0= no; 1= yes; If yes, please explain under description

As a result of the event, administration of the BI product was: 1= continued; 2= reduced; 3= discontinued; 4 = increased; 5= terminated in line with observational plan; 6= discontinued and resumed; 7 = not applicable

Outcome of the event: 1= recovered; 2= not yet recovered; 3= permanent damage; 4= fatal; 5= unknown

Was the event serious? ** If fatal, please attach copy of death certificate

Causal relationship: Is there a justified suspicion of a causal relationship between the event and the use of Pradaxa®

Is the event expected (listed / expected) ?

	Start date (Day/Mon/Year)	Time in hh:mm (24-hr clock)	End date (Day/Mon/Year)	Time in hh:mm (24-hr clock)	Intensity	Therapy	As a result of the event, administration of the BI product was	Outcome	Was the event serious? 0 = no, 1 = yes	If yes, enter the corresponding code number: 1= fatal**; 2= immediately life-threatening; 3= permanent or significant disability/ incapacity; 4= requires hospitalisation; 5= prolongs hospitalisation; 6= congenital abnormality; 7= other / further comparable medical criteria, e.g. drug dependence, abuse, cancer, etc.)	Causal relationship: Reporter 0= no 1= yes	Causal relationship: PV Ger 0= no 1= yes	Is the event expected (listed / expected) ? PV Ger 0= no 1= yes
1.													
2.													
3.													
4.													

Description of the events listed above (if necessary, please give the number of the event as in the above table, Event column):

_____

Please send immediately to Boehringer Ingelheim Pharma GmbH & Co KG on Fax No. 06132-72-141522 or PV_Germany.de@boehringer-ingelheim.com. Leave shaded areas blank.

Boehringer Ingelheim **Site number:** |__|__|__|__|	**Report of Serious/Non-Serious Adverse Events in Non-Interventional Study (NIS)** **NIS title: 1160.218 / Pradaxa®**	OPU case ID number: Pat. initials: |__|__|__| Pat. No.: |__|__|	**BI CTMS number:** **1160.218**

Drug / therapy If medicinal product, give proprietary and common name	Pharma-ceutical form	Total daily dose at start (dose, unit)	Route of administration	Start (date) Day / Month / Year	End (date) Day / Month / Year	Given for which indication?	Other suspect drug: is there a causal relationship between event and concomitant therapy?	
Boehringer Ingelheim medication **Pradaxa®**							**Reporter:** **0= no** **If yes,** enter number of event	**PV Ger:** **0= no** **If yes,** enter number of event
Concomitant therapy (relevant) 1.								
2.								
3.								
4.								

Concurrent diagnoses (relevant):

1._____
2._____
3._____

Comments (surrounding circumstances, alternative explanation of the event, where applicable re-exposure, etc.)

_____
_____

Name of reporter:

_____

Signature

Date
____/____/____
Day / Month / Year

Boehringer Ingelheim

Observational Plan
Non-interventional study
Local Amendment

Local Amendment Number:	Local Amendment 1 Country Germany		
Date:	16. APR 2015	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.:	n.a.	☐	To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval
BI Trial No.:	1160.218		
Investigational Product(s):	Pradaxa®	X	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only
Title:	Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)		
Rationale for Local Amendment:	After 6 months of site and patient recruitment it became evident that the targeted patient and site numbers will not be met and that recruitment time should be longer. Therefore the planned patient number will be reduced to 1600 and site number to 800. Recruitment time will be prolonged to 16 months (LPI December 2015), thus study duration will also increase. LPO is now planned for December 2016. Other timelines will change accordingly. New site and patient numbers will be used as calculation basis in the statistical analysis plan. As this amendment is administrative and does not change the content or the nature of this non-interventional study, for readability reasons we refrain from changing every sentence in which site numbers, patient numbers or timelines are mentioned, except for the front page, study synopsis and statistics section.		

SIGNATURE PAGE(S)

This amendment

☒ concerns administrative matters only so that the coordinating investigator's signature will not be obtained.

☐ concerns matters dealing with design elements of the study, in- / exclusion criteria, observations, or safety or efficacy related study elements so that the coordinating investigator's signature needs to be obtained.

Trial Clinical Monitor

May 06 2015
Date

Trial Statistician

Date

Boehringer Ingelheim
Biometrics & Data
Management

Team Member Medicine

Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

May 06 2015
Date

Boehringer Ingelheim
Medical Affairs Germany

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Trial Clinical Monitor

May 06 2015
Date

Trial Statistician

May 07 2015
Date

Boehringer Ingelheim
Biometrics & Data
Management

Team Member Medicine

Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

May 06 2015
Date

Boehringer Ingelheim
Medical Affairs Germany

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Trial Clinical Monitor

May 06 2015

Date

Trial Statistician

Date

Boehringer Ingelheim
Biometrics & Data
Management

Team Member Medicine

7.5.2015

Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

May 06 2015

Date

Boehringer Ingelheim
Medical Affairs Germany

CHANGE 1: ADAPT TIME SCHEDULE, SITE NUMBERS AND PATIENT NUMBERS

Section of the protocol: Front page

Scheduled time frame of the NIS:	FPI September 2014	LPO April 2016

Was changed to:

Scheduled time frame of the NIS:	FPI September 2014	LPO December 2016

Reasons for change 1:

After 6 months of site and patient recruitment it became evident that the targeted patient and site numbers will not be met and that recruitment time should be longer.

Recruitment time will be prolonged to 16 months (LPI December 2015), thus study duration will also increase. LPO is now planned for December 2016.

CHANGE 2: ADAPT TIME SCHEDULE, SITE NUMBERS AND PATIENT NUMBERS

Section of the protocol: Synopsis

Target group (sites)	1000: about 670 community-based primary care internists or general practitioners and 330 cardiologists
	• In this NIS, information about dabigatran etexilate/VKA persistence and adherence will be collected in 4000 AF patients.
Number of patients:	4000; 2000 on dabigatran etexilate; 2000 on VKA
Scheduled study duration	Initiation (FPI): September 2014 Last patient out (LPO): April 2016
Report	Report available: July 2016

Was changed to:

Target group (sites)	800: about 550 community-based primary care internists or general practitioners and 250 cardiologists
	• In this NIS, information about dabigatran etexilate/VKA persistence and adherence will be collected in 800 AF patients.
Number of patients:	Approx. 1600; Approx. 800 on dabigatran etexilate; approx. 800 on VKA
Scheduled study duration	Initiation (FPI): September 2014 Last patient out (LPO): December 2016
Report	Report available: March 2017

Reasons for change 2:

After 6 months of site and patient recruitment it became evident that the targeted patient and site numbers will not be met and that recruitment time should be longer.

Therefore the planned patient number will be reduced to 1600 and site number to 800.

Recruitment time will be prolonged to 16 months (LPI December 2015), thus study duration will also increase. LPO is now planned for December 2016.

Other timelines will change accordingly.

CHANGE 3: ADAPT TIME SCHEDULE, SITE NUMBERS AND PATIENT NUMBERS

Section of the protocol: Statistics Section Determination of number of patients

It is planned to include a total of 4000 patients in this non-interventional, controlled, observational study (dabigatran etexilate: 2000 patients, VKA: 2000 patients).

Calculation of statistical power:
All analyses are purely exploratory by virtue of the non-interventional study design. On the following assumptions:

- 15% drop-outs /missing values after one year,
- 2000 dabigatran etexilate patients, 2000 VKA patients, with 66% of VKA patients with a matching partner in the dabigatran etexilate group
  (i.e. total number of patients in the 1:1 matched analysis is **2640**)
- a persistence rate of 63% in the dabigatran etexilate group (cf. 1-year persistence with a 60-day permissible medication gap as reported by Zalesak ([19])).

the power for a descriptive p value <=0.05 in a 2-tailed test for the same persistence rates is as follows (dependent on the VKA persistence rate):

Assumed VKA persistence rate*	**51%**	**53.8%**	**56.5%**
Power	100%	99.7%	91.7%

* The calculations were performed with ADDPLAN6 and are based on survival time analysis test statistics and the endpoint variables "Time to permanent treatment discontinuation".

Was changed to:

It is planned to include a total of 1600 patients in this non-interventional, controlled, observational study (dabigatran etexilate: 800 patients, VKA: 800 patients).

Calculation of statistical power:
All analyses are purely exploratory by virtue of the non-interventional study design. On the following assumptions:

- 15% drop-outs /missing values after one year,
- 800 dabigatran etexilate patients, 800 VKA patients, with 66% of VKA patients with a matching partner in the dabigatran etexilate group
  (i.e. total number of patients in the 1:1 matched analysis is **1056**)
- a persistence rate of 63% in the dabigatran etexilate group (cf. 1-year persistence with a 60-day permissible medication gap as reported by Zalesak ([19])).

the power for a descriptive p value <=0.05 in a 2-tailed test for the same persistence rates is as follows (dependent on the VKA persistence rate):

Assumed VKA persistence rate*	**51%**	**53.8%**	**56.5%**
Power	97.8%	84.8%	61.1%

* The calculations were performed with ADDPLAN6 and are based on survival time analysis test statistics and the endpoint variables "Time to permanent treatment discontinuation".

Reasons for change 3:

After 6 months of site and patient recruitment it became evident that the targeted patient and site numbers will not be met and that recruitment time should be longer.

Therefore the planned patient number will be reduced to 1600 and site number to 800.

Boehringer Ingelheim

Observational Plan
Non-interventional study
Local Amendment

[redacted]

Local Amendment Number:	Local Amendment 2 Country Germany		
Date:	04. JAN 2016	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.:	n.a.	☐	To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval
BI Trial No.:	1160.218		
Investigational Product(s):	Pradaxa®	X	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only
Title:	Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)		
Rationale for Local Amendment:	After 15 months of patient recruitment 1050 / 1600 patients have been included until December 2015. For a meaningful data analysis and interpretation, the targeted patient number of 1600 patients should be met. Therefore, recruitment time will be prolonged for one more year to 27 months (LPI December 2016), thus study duration will also increase. LPO is now planned for December 2017. Other timelines will change accordingly. In case 1600 patients will be included earlier, recruitment may be stopped before December 2016. As this amendment is administrative and does not change the content or the nature of this non-interventional study, for readability reasons we refrain from changing every sentence in which site numbers, patient numbers or timelines are mentioned, except for the front page, study synopsis and statistics section.		

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Trial Clinical Monitor

14.01.16
Date

Boehringer Ingelheim
Medical Affairs Germany

Trial Statistician

_____ _____
Date

Boehringer Ingelheim
Biometrics & Data Management

Team Member Medical Affairs

18-01-2016
Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

14.01.16
Date

Boehringer Ingelheim
Medical Affairs Germany

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Trial Clinical Monitor

14.01.16
Date

Boehringer Ingelheim
Medical Affairs Germany

Trial Statistician

14.01.16
Date

Boehringer Ingelheim
Biometrics & Data
Management

Team Member Medical Affairs

18-01-2016
Date

Boehringer Ingelheim
Corporate Medical Affairs

Local Clinical Monitor

14.01.16
Date

Boehringer Ingelheim
Medical Affairs Germany

CHANGE 1: ADAPT TIME SCHEDULE, SITE NUMBERS AND PATIENT NUMBERS

Section of the protocol: Front page

Scheduled time frame of the NIS:	FPI September 2014	LPO April 2016

Was changed to:

Scheduled time frame of the NIS:	FPI September 2014	LPO December 2017

Reasons for change 1:

After 15 months of patient recruitment 1050 / 1600 patients have been included until December 2015. For a meaningful data analysis and interpretation, the targeted patient number of 1600 patients should be met.

Therefore, recruitment time will be prolonged for one more year to 27 months (LPI December 2016), thus study duration will also increase. LPO is now planned for December 2017.

In case 1600 patients will be included earlier, recruitment may be stopped before December 2016.

CHANGE 2: ADAPT TIME SCHEDULE, SITE NUMBERS AND PATIENT NUMBERS

Section of the protocol: Synopsis

Scheduled study duration	Initiation (FPI): Last patient out (LPO):	September 2014 April 2016
Report	Report available:	July 2016

Was changed to:

Scheduled study duration	Initiation (FPI): Last patient out (LPO):	September 2014 December 2017
Report	Report available:	March 2018

Reasons for change 2:

After 15 months of patient recruitment 1050 / 1600 patients have been included until December 2015. For a meaningful data analysis and interpretation, the targeted patient number of 1600 patients should be met.

Therefore, recruitment time will be prolonged for one more year to 27 months (LPI December 2016), thus study duration will also increase. LPO is now planned for December 2017.

Other timelines will change accordingly.

In case 1600 patients will be included earlier, recruitment may be stopped before December 2016.