Non Interventional Study Protocol Amendment

BI Study No.:	1160.139
BI Investigational Product(s):	Dabigatran etexilate mesilate
Title:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Pradaxa (Dabigatran etexilate mesilate, 110 mg or 150 mg b.i.d.) in Korean patients with non-valvular atrial fibrillation (SPARK: Safety study of Pradaxa in AF patients by Regulatory requirement of Korea)
Clinical Phase:	IV
Trial Clinical Monitor:	[redacted] Phone [redacted] Fax: [redacted]
Principal Investigator:	Not applicable
Status:	*Final protocol amendment IV*
Version and Date:	**Version: 4.0 Date: 10 June 2013**

TITLE PAGE

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: Pradaxa			
Name of active ingredient: Dabigatran etexilate mesilate			
Protocol date: 29 April 2011	**Trial number:** 1160.139		**Revision date:** 10 June 2013

Title of study:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Pradaxa (Dabigatran etexilate mesilate, 110 mg or 150 mg b.i.d.) in Korean patients with non-valvular atrial fibrillation (SPARK: Safety study of Pradaxa in AF patients by Regulatory requirement of Korea)
Principal Investigator:	Not Applicable
Study site(s) :	Multi-centre study
Clinical phase:	IV
Objectives:	To monitor the safety profile and effectiveness of dabigatran etexilate mesilate in patients with non-valvular atrial fibrillation in a routine clinical practice setting
Methodology:	Prospective, non-interventional, open-label, multi-centre national study
No. of patients:	
Total entered:	3,000 approximately No. of patients for short-term surveillance: 1,500 No. of patients for long-term surveillance: 1,500
each treatment:	Single arm (N=3,000 approximately)
Diagnosis:	Patients diagnosed with non-valvular atrial fibrillation and at risk of stroke or systemic embolism
Main criteria for inclusion:	1) Age ≥ 18 years at enrollment 2) Patients who have been started on Pradaxa in accordance with the approved label in Korea 3) Patients who have signed on the data release consent form

Name of company/Marketing Authorisation Holder: Boehringer Ingelheim Korea		**Tabulated Study Protocol**	
Name of finished product: Pradaxa			
Name of active ingredient: Dabigatran etexilate mesilate			
Protocol date: 29 April 2011	**Trial number:** 1160.139		**Revision date:** 10 June 2013

Main criteria for exclusion:

1) Patients with previous exposure to Pradaxa
2) Clinically significant bleeding
3) Increased risk of bleeding due to following diseases;
   - Recent gastrointestinal ulceration
   - Recent intracranial or intracerebral bleeding history
   - Intraspinal or intracerebral vascular abnormalities
   - Recent brain, spinal or ophthalmic surgery
   - Recent brain or spinal injury
   - Known or suspected oesophageal varices
   - Arteriovenous malformations
   - Vascular aneurysms
   - Presence of malignant neoplasms at high risk of bleeding
4) Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
5) Severe renal impairment (CrCl < 30mL/min)
6) Concomitant treatment with oral ketoconazole or dronedarone
7) Patients hypersensitive to dabigatran or dabigatran etexilate or to any ingredient in the formulation
8) Prosthetic heart valve replacement
9) No creatinine clearance collected within at least one year prior to enrollment
10) Current participation in other clinical trials

Test product(s) : Dabigatran etexilate mesilate

dose: 110 mg b.i.d., 150 mg b.i.d.

mode of admin. : Oral administration

Comparator product(s): Not applicable

dose:

mode of admin. :

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Duration of treatment:	1) Treatment duration for short-term surveillance: 12±2 weeks, long-term surveillance: 24±2 weeks 2) Study duration: 6 years (Study period required by the Ministry of Food and Drug Safety (MFDS) is from 18 Feb 2011 to 17 Feb 2017. Interim reports are expected biannually for the initial two years and annually thereafter by May 2017.)
Criteria for effectiveness:	Incidence of stroke or systemic embolism
Criteria for safety:	All reported adverse events in patients who have taken at least one dose of Pradaxa will be noted.
Statistical methods:	Descriptive statistics

FLOW CHART

Data points	**Baseline**	**Follow-up 1(Short-term)**	**Follow-up 2(Long-term)**
Visit Number	1	2	3
Week/s	0	12±2	24±2
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Renal Function	X		
Lifestyle factors	X		
AF disease characteristics	X		
Medical history	X		
Anti-thrombotic therapy	X	X	X
Concomitant medications	X	X	X
Pradaxa administration status	X	X	X
Vital signs	X	X	X
Effectiveness endpoints		X	X
Changes in lab tests together with action on drugs		X	X
Adverse events		X	X
Treatment compliance		X	X
Study completion		X	X

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ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
aPTT	Activated Partial Thromboplastin Time
ASA	Acetyl Salicylic Acid
CA	Competency Authority
CABG	Coronary Artery Bypass Graft
CHF	Congestive Heart Failure
CK-MB	Creatinine Kinase-Myocardial Band
CML	Clinical Monitor Local
CRF	Case Report Form
CRO	Contract Research Organization
CSO	Clinical Safety Officer
CT	Computed Tomography
eCRF	Electronic Case Report Form
ECG	Electrocardiograph
EDC	Electronic Data Capture
FU	Follow up
KIMS	Korea Index of Medical Specialties
KPAC	Korean Pharmaceutical Affairs Code
KPMA	Korea Pharmaceutical Manufacturers Association
KRPIA	Korean Research-based Pharmaceutical Industry Association
GCP	Good Clinical Practice
LVD	Left Ventricular Dysfunction
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFDS	The Ministry of Food and Drug Safety
MR	Magnetic Resonance
mRS	Modified Rankin Scale
NCE	New Chemical Entity
NIS	Non-Interventional Study
PCI	Percutaneous Coronary Intervention
PMS	Post Marketing Surveillance study
SAE	Serious Adverse Event
TIA	Transient Ischemic Attack
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
VKA	Vitamin K antagonist

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in the community and affects approximately 12% of population (R03-1233). It is estimated that 6 million people in Europe and 2.7 million people in the USA suffer from AF (P10-10141, P06-08196). The lifetime risk for the development of AF is one in four for those over the age of 40 years (R09-4884). In Korea, the number of patients visited hospital for AF or atrial flutter was 80,000, approximately, according to the 2009 National Health Insurance Statistical Yearbook.[1] On average, the number of patients diagnosed with AF between 2001~2004 was 52,025 and AF prevalence in the age over 60 and over 70 was 1.95% and 2.41%, respectively, according to the KORAF (KORean Atrial Fibrillation Registry).[2]

The prevalence of AF rises with advancing age, increasing from less than 1% in those under 60 years of age to nearly 20% in those aged 85 years or more (R09-4875). The overall prevalence of AF in hospital setting is also increasing; hospital admissions due to AF have increased by 60% over the past 20 years (R10-1345). Furthermore, the prevalence of AF is estimated to double by 2050 due to the aging of the world's population (R03-1233).

Thromboembolic complications, particularly strokes, are a major cause of morbidity and mortality in patients with AF. Most of the strokes associated with AF are due to distal embolization of a left atrial thrombus, particularly arising from the left atrial appendage. Patients with AF have a four to five fold higher risk of stroke than those without AF (R96-0252, R03-1241). Furthermore, approximately 15% of all strokes are directly attributed to AF and patients with strokes associated with AF have worse outcome with higher mortality than those with strokes not associated with AF (R09-4892).

The risk of stroke or systemic embolism in patients with AF is influenced by other vascular risk factors including the history of previous strokes or transient ischemic attacks (TIA), hypertension, left ventricular dysfunction (LVD), congestive heart failure (CHF), advanced age, diabetes mellitus, and coronary artery disease. Patients without any of these risk factors, i.e., lone AF, have a lower likelihood for the occurrence of stroke, thromboembolic events and stroke-related mortality (R03-1229, P06-08196, and R03-1241). The classic $CHADS_2$ (Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischemic attack, see Appendix 10.1) score is a risk score that was developed as a simple method for clinicians to assess the risk of stroke and thromboembolism in patients with AF (P06-10925). Given that the $CHADS_2$ score does not include many stroke-related risk factors, a modification has been developed (CHA_2DS_2-VASc score, see Appendix 10.1) to improve its predictive value of stroke and thromboembolic events (R10-5332, P10-10141).

Strokes due to AF are partly preventable by antithrombotic therapy. A meta-analysis of controlled clinical trials demonstrated that warfarin decreased the risk of stroke/systemic embolism, on average, by 62% versus placebo, while antiplatelet therapy reduced the occurrence of stroke by 22% compared to placebo. However when the analysis was confined to aspirin only trials, aspirin reduced stroke by a non-significant 19% (95% CI: -1% to 35%)

compared to placebo (P07-07953, R03-1227). Oral anticoagulation with vitamin K antagonists (VKAs, e.g. warfarin) is the current standard therapy for stroke prevention in AF patients with moderate to high-risk of stroke (P10-10141, P07-04925, P06-08196, P10-00811). However, VKAs have clinically important limitations including a narrow therapeutic window, an unpredictable dose-response effect, numerous drug-drug and drug-food interactions, and slow onset and offset of action. As a result, many patients with AF do not receive VKAs and instead receive ASA, antiplatelet agents, both or no antithrombotic therapy (R03-1241). Even when VKAs are used, regular anticoagulation monitoring and dose adjustments are needed to achieve effective anticoagulation.

In a real-life setting, VKA treatment often results in INR (International Normalized Ratio) values outside of the target therapeutic range (R10-0768, R09-1522), leaving patients at increased risk of either stroke or bleeding. Due to the clinical and practical limitations of VKAs, multiple new oral anticoagulants are in clinical development including, mainly, direct thrombin inhibitors and factor Xa inhibitors (P07-08370). Pradaxa (dabigatran etexilate mesilate), a direct thrombin inhibitor, has been approved for the risk reduction of stroke or systemic embolism in patients with AF since February 2011, in Korea. In a clinical trial involving l18,113 patients, compared to warfarin, dabigatran etexilate mesilate (150 mg b.i.d.) reduced the occurrence of stroke (both ischemic and hemorrhagic) and systemic embolism significantly, while the rate of major bleeding was similar with both treatment. RE-LY (P09-11669). Furthermore, dabigatran etexilate mesilate (110 mg b.i.d.) was found to be non-inferior to warfarin for the prevention of stroke or systemic embolism while resulting in fewer major bleeds. Importantly, both doses of dabigatran etexilate mesilate were associated with significantly reduced occurrence of intracranial haemorrhage compared to warfarin (P09-11669).

1.2 DRUG PROFILE

Dabigatran etexilate mesilate is the orally bioavailable prodrug of dabigatran, a novel, synthetic, direct thrombin inhibitor. Dabigatran etexilate mesilate itself does not have any antithrombin activity. Following oral administration it is rapidly converted via serum esterase to the active moiety, dabigatran, which is a non-peptidic, potent, competitive, and reversible inhibitor of thrombin. (U98-3208)

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE STUDY

According to the local regulations, when a new chemical entity (NCE) is registered, a post marketing surveillance study (NIS) of an extended period (4 or 6 years) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomised clinical trials with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

This is a prospective, non-interventional, open-label, multi-centre study. It will provide additional safety information of Pradaxa in Korean patients with non-valvular AF in clinical settings.

2.2 STUDY OBJECTIVES

2.2.1 Primary objective

The primary objective of this study is to monitor the safety profile of Pradaxa in Korean patients with non-valvular AF in a routine clinical setting.

2.2.2 Secondary objective

The secondary objective of the study is to monitor the effectiveness of Pradaxa in reducing the risk of stroke or systemic embolism in Korean patients with non-valvular AF, by observing the incidence of stroke or systemic embolism.

2.3 BENEFIT-RISK ASSESSMENT

Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. Pradaxa will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this NIS.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL DESIGN AND PLAN

This NIS is a prospective, non-interventional, open-label, multi-centre study. As per regulation, the re-examination period extends from 18 Feb 2011 until 17 Feb 2017 (6 years). However, active enrolment is to be initiated in 2012 after finalizing the re-imbursement agreement with the authority. Before initiation of the study, any newly reported adverse events will be closely monitored. The last patient follow up is expected in 2015.

3.1.1 Administrative structure of the study

This study will be managed by a project manager of Boehringer Ingelheim Korea. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

3.2 DISCUSSION OF STUDY DESIGN

This is a single arm study with dabigatran etexilate mesilate cohort.

Loss to follow up

All efforts will be made to minimize loss to follow up, particularly in the tracking of lost patients. To the extent possible, vital status, at minimum, for patients lost to follow up will be obtained. This allows assessing the impact of informative censoring due to treatment discontinuation. Also, patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if dabigatran would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events were then expected in the dabigatran group.

Information and recall bias

Information bias can e.g. occur due to selective reporting of already established and known adverse effects for a known product as compared to a new product (dabigatran), or vice versa. A standardized data collection form will be used for assessing exposure and AEs. These standardized procedures for data collection are intended to minimize such biases. Recall bias may be caused, e.g. if visits are separated by long time intervals and patient forget certain information. It can be reduced by associating questions with specified time intervals (e.g. how often did you take this co-medication *during the last 5 days)*.

Confounding

As in any observational study, confounding may affect the estimation of associated between drug exposure and outcome of interest and statistical techniques. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

3.3 SELECTION OF POPULATION

Minimum 3,000 patients will be enrolled at approximately 40 sites by as many as 80 or more investigators. The treating physicians will mainly be cardiologists or neurologists. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

3.3.1 Main diagnosis for study entry

Patients diagnosed with non-valvular AF and at risk of stroke or systemic embolism will be included. Physician should carefully review the product label in Korea before prescribing Pradaxa to patients (Attachment 4). Updated label information is found in eCRF and ISF (Investigator Site File). The exclusion criteria reflect the contraindication of the product label. Thus if the contraindication section of the label is updated, the physician should follow the up-to-date prescribing information ahead of the inclusion / exclusion criteria of this protocol.

3.3.2 Inclusion criteria

- Age ≥ 18 years at enrollment
- Patients who have been started on Pradaxa in accordance with the approved label in Korea
- Patient who has signed on the data release consent form

3.3.3 Exclusion criteria

- Patients with previous exposure to Pradaxa
- Clinically significant bleeding
- Increased risk of bleeding due to following diseases;

  Recent gastrointestinal ulceration

  Recent intracranial or intracerebral bleeding history

  Intraspinal or intracerebral vascular abnormalities

  Recent brain, spinal or ophthalmic surgery

Recent brain or spinal injury

Known or suspected oesophageal varices

Arteriovenous malformations

Vascular aneurysms

Presence of malignant neoplasms at high risk of bleeding

- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- Severe renal impairment (CrCl < 30mL/min)
- Concomitant treatment with oral ketoconazole or dronedarone
- Patients hypersensitive to dabigatran or dabigatran etexilate or to any ingredient in the formulation
- Prosthetic heart valve replacement
- No creatine clearance collected within at least one year prior to enrollment
- Current participation in other clinical trials

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients (therapy or assessments)

This section is not applicable.

3.3.4.2 Discontinuation of the study by the sponsor

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

1. Emergence of any efficacy/safety information that could significantly affect continuation of the study
2. Violation of applicable local regulations, the NIS protocol, or the contract by a study site or participating physician, disturbing the appropriate conduct of the study.

4. TREATMENTS

4.1 PRESCRIBED TREATMENTS TO BE OBSERVED

4.1.1 Identity of the product(s)

Pradaxa will be prescribed according to the local label and at the discretion of the treating physician. Since this is a non-interventional study, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic tests.

4.1.2 Method of assigning patients to treatment groups

The choice of treatment is fully at the discretion of the physician and the patient. There is no treatment assignment by a third party.

4.1.3 Selection of doses in the study

The choice of dabigatran dose, from those two options described below, should be determined according to the local label (attachment 4) and at the discretion of the treating physician. Physician should carefully review the special precautions for use in patients with risk of bleeding (Attachment 5) before determining the dose of Pradaxa.

- Dabigatran etexilate mesilate 110 mg b.i.d. (one capsule twice daily)
- Dabigatran etexilate mesilate 150 mg b.i.d. (one capsule twice daily)

4.1.4 Drug assignment and administration of doses for each patient

This section is not applicable.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

The protocol will allow additional drugs considered necessary for the patient's welfare to be prescribed at the discretion of the treating physician. It is required, however, to record the details of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Pradaxa initiation until the patient completes the final follow-up visit.

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Please refer to the current local label (Attachment 4).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Please refer to the current local label (Attachment 4).

4.2.2.2 Restrictions on diet and life style

Please refer to the current local label (Attachment 4).

4.3 TREATMENT COMPLIANCE

During the follow-up visits, treatment compliance will be evaluated by treating physician. To minimize the recall bias, the physician could ask associating questions with specified time intervals (e.g. how often did you take Pradaxa *during the last 5 days*) to patients. An explanation for any discrepancy will be inquired and provided in the eCRF.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFECTIVENESS

5.1.1 Endpoint(s) of effectiveness

The effectiveness endpoint is the incidence rate of stroke or systemic embolism (definitions are provided in Section 5.1.2.)

5.1.2 Assessment of effectiveness

Since the patient follow-up period is only 12 weeks (in case of long-term FU, 24 weeks), it is not possible to perform any meaningful effectiveness assessment of Pradaxa in this NIS. However, since it is a requirement to evaluate also effectiveness in all regulatory requisite NIS in Korea and as requested by MFDS, a descriptive analysis of effectiveness endpoint will be performed.

Effectiveness analysis will be performed to the patients who have been on Pradaxa more than 12 weeks (in case of long-term FU, 24 weeks).

The following definitions apply and should be used as a guide when reporting a thrombotic event:

Stroke:

Stroke is an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke is categorized as ischemic or hemorrhagic or uncertain classification (based on CT or MR scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin Scale (see Table 10.1:4) at discharge from hospital and/or at 3-6 months later (if available).

Systemic embolism:

Systemic embolism is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), typically documented by angiography, surgery, scinitigraphy, or autopsy.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

All reported adverse events in patients who take at least one dose of Pradaxa will be noted.

Endpoints pertaining to safety will be presented descriptively and will include:

- adverse events

- unexpected adverse events
- serious adverse events
- drug-related adverse events
- adverse events leading to discontinuation
- adverse events by intensity, outcome of the event, causality

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

The following definitions apply and should be used as a guide when reporting a thrombotic event:

Transient ischemic attack (TIA)

TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction (P11-00444).

Pulmonary embolism

- A patient has to fulfil the following criteria:

1. Typical symptoms or signs (e.g., dyspnea, left or right sided chest pain worsening on respiration, etc) suggestive of pulmonary embolism

AND at least one of the following two criteria:

2. CT pulmonary angiography demonstrating an intraluminal filling defect in segmental or more proximally located pulmonary arteries

3. High probability ventilation-perfusion lung scan, i.e. at least segmental perfusion defect at perfusion scan with normal ventilation at ventilation scan

- The definition of pulmonary embolism is also met if a patient fulfils at least criteria 2) or 3) above.

Myocardial infarction:

- In patients not undergoing PCI or CABG: A patient has to fulfil either the criteria:

  - Development of significant Q-waves in at least 2 adjacent ECG leads.

  Or at least 2 of the following three criteria:

  - Typical prolonged severe chest pain of at least 30 min
  - ECG changes suggestive of myocardial infarction including ST-changes of T-wave inversion in the ECG.
  - Elevation of troponin or CK-MB to more than upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.

- After PCI (within 24h)

  Elevation of troponin or CK-MB* to more than 3xULN or, if CK-MB is elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or developing of significant Q-waves** in at least two adjacent ECG leads.

- After coronary artery bypass grafting (within 72h)

  Elevation of CK-MB* to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves** in at least two adjacent ECG leads.

*Total CK if CK-MB was not available **A new Q-wave with a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

Major bleeding, defined as meeting one or more of the following criteria (R11-1250, P11-05406):

- Overt bleeding associated with a reduction in haemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding
- Life-threatening bleeding
- Fatal bleeding

Life-threatening bleeding, as defined as meeting one or more of the following criteria:

- Symptomatic intracranial bleed
- Reduction in haemoglobin of at least 50 grams per liter
- Transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents
- Necessitated surgical intervention

Deaths

will be classified as being: vascular (including bleeding); non-vascular, due to other specified causes (e.g., malignancy), or unknown cause, when cause is not known.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Always serious adverse events

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these “always serious adverse events”, if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item “serious” needs to be ticked and an SAE has to be reported in expedited fashion. The list of these adverse events can be found via the eCRF system.

Adverse drug reaction

Adverse drug reaction (ADR) refers to any harmful, unintended reaction to the pharmaceutical product of any dose at which a causal relationship with the pharmaceutical product cannot be ruled out.

Non serious adverse drug reaction

Non serious adverse drug reaction is defined as any ADR which does not meet the SAE criteria.

Intensity of adverse event

The intensity of the AE should be defined based on the following three categories and according to medical and scientific judgment:

Mild:	Transient symptoms which are subjective or objective but no interference with the patient's daily activities. No change in dosage is needed to continue the treatment.
Moderate:	Marked symptoms with moderate interference with the patient's daily activities. Reduced dosage or unplanned treatment is necessary for the relief of adverse events.
Severe:	Considerable and unacceptable interference with the patient's daily activities. Discontinuation of the study drug is required because of significant adverse events.

To ensure that no confusion or misunderstanding of the difference between the terms 'serious' and 'severe' which are not synonymous, it should be noted that SAE does not necessarily correspond to serious or not serious AE to severe ones. All SAEs will be reported regardless of the intensity as mentioned above.

Causal relationship of adverse event

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

Related

a. Certain: An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

b. Probable/Likely: An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible: An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unrelated

d. Unlikely: An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

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

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the NIS physician.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events occurring from the start of Pradaxa treatment up to 7 days after last follow-up visit need to be collected, documented and reported to the sponsor using the AE reporting form of eCRF (Attachment 1). All SAEs must be reported with details of non-serious AEs occurring at the same time, within 24 hours of occurrence via telephone/fax to the Clinical Safety Officer (CSO) of BI Korea using the SAE report form (Attachment2). If any new or further information to these events is available, a follow-up SAE report has to be sent to BI. All SAEs and non-serious AEs must include a causal relationship assessment from the physician.

All other Adverse Events must be reported on the eCRFs within 2 weeks to the Sponsor.

Contact details:

Clinical Safety Officer

Tel: +82.2.709.0171

Fax: +82.2.749.0062

Address: Boehringer Ingelheim Korea, Medical Dept.

15F, Yonsei Severance Bldg. 84-11, Namedaemunro-5Ka, Chung-Ku, Seoul, Korea

Pregnancy

Rarely, patients taking part in non interventional studies can get pregnant. Once a patient enrolled into the study and exposed to Pradaxa becomes pregnant, the NIS physician will stop the drug and report immediately to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day, whichever is shorter) to CSO. Furthermore, the details of all the drugs to which the patient exposed at the time of pregnancy will be recorded. The outcome of the pregnancy associated with the drug exposure will be assessed. In the absence of an (S)AE, only the Pregnancy Monitoring Form (Attachment 3) for NIS, not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form (Part A and Part B) and those forms could be downloaded from eCRF website.

5.2.3 Assessment of safety laboratory parameters

This section is not applicable.

5.2.4 Electrocardiogram

This section is not applicable.

5.2.5 Assessment of other safety parameters

This section is not applicable.

5.3 OTHER

This section is not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

This section is not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The flow chart at the front of the protocol summarizes the data to be collected at each visit. The procedures are further described below.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

This section is not applicable as this is a non-interventional study.

6.2.2 Treatment period(s)

As per regulations, enrolled patients will be followed up for a 12 week or 24 week treatment period. There will be a visit window of ±2 weeks. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for short-term or long-term surveillances.

6.2.2.1 Visit 1 – Baseline Visit

Upon patient enrollment, the following will be recorded on the patient's eCRF.

- Visit date
- Diagnosis: date of the diagnosis and the diagnostic procedures performed
- Inclusion / exclusion criteria
- Demographic data: date of birth, gender, pregnancy, previous allergy, height, weight
- Renal function: record creatinine clearance collected within at least one year prior to enrolment
- Lifestyle factors: smoking habits and alcohol use
- Atrial fibrillation disease characteristics: categorization, type, procedures since confirmation of AF diagnosis
- Medical history: history of thromboembolic episodes, cardiovascular diseases, history of bleeding events, other relevant medical history
- Anti-thrombotic therapy: record all the anti-thrombotic therapy received since one month prior to the baseline visit (excluding Pradaxa)
- Concomitant medications: record all medications as well as continuous medications since one month prior to the baseline visit except for anti-thrombotic therapy (but including vitamins and food supplements)
- Dose of Pradaxa given
- Vital signs: average blood pressure (sitting arm) and pulse rate

At Visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating Pradaxa treatment.

6.2.2.2 Visit 2 (12±2 weeks from Visit 1)

After 12±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

- Visit date
- Any change of Pradaxa dose given
- Any changes in laboratory tests which required actions on drug dosage since last visit or any laboratory values performed to monitor the increased risk of bleeding ie. aPTT
- Vital signs: average blood pressure (sitting arm) and pulse rate
- Effectiveness endpoints: incidence of stroke or systemic embolism
- Anti-thrombotic therapy: any change in the anti-thrombotic therapies since last visit (excluding Pradaxa)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Treatment compliance
- Study completion status: for the prematurely withdrawn patients, this section should be recorded to assess the safety information and the reason for withdrawal
- NIS physician's electronic signature for data integrity (do not record this section for long-term FU cases)

At Visit 2, the patients on long-term follow-up will be reminded to contact the NIS physician in the event of any adverse events noted hereafter.

6.2.2.3 Visit 3 (24±2 weeks from Visit 1, Long-term follow-up cases only)

After 24±2 weeks from Visit 1 or 12±2 from Visit 2, the patients will return for follow-up. The followings will be noted and recorded in the eCRF:

- Visit date
- Any change of Pradaxa dose given
- Any changes in laboratory tests which required actions on drug dosage since last visit or any laboratory values performed to monitor the increased risk of bleeding ie. aPTT
- Vital signs: average blood pressure (sitting arm) and pulse rate
- Effectiveness endpoints: incidence of stroke or systemic embolism
- Anti-thrombotic therapy: any change in the anti-thrombotic therapies since last visit (excluding Pradaxa)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Treatment compliance
- Study completion status: for the prematurely withdrawn patients, this section should be recorded to assess the safety information and the reason for withdrawal
- NIS physician's electronic signature for data integrity

6.2.3 End of trial and follow-up period

For patients prematurely withdrawn from the study, it is important to collect the safety information whether or not any adverse event occurred after administration of Pradaxa and reflect the information in the eCRF section of "study completion status". Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of Pradaxa will be monitored further until the resolution of those adverse events. Alternatively, those

patients will be followed up until the NIS physician and sponsor agree that no further follow-up is necessary. To the extent possible, vital status, at minimum, for patients lost to follow up will be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details are provided in the statistical Trial Statistical Analysis Plan (TSAP).

7.1 STATISTICAL DESIGN - MODEL

In this non-interventional study, all statistical analyses will be descriptive in nature. The degree of statistical significance (p-values) and precision (confidence intervals) for the statistical methods used for explorative purposes will be shown. No confirmatory hypotheses are pre-specified.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No hypotheses are tested. (See Section 7.1)

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

A descriptive analysis of effectiveness endpoints is planned. For patients treated with Pradaxa incidence of stroke or systemic embolism will be calculated. Effectiveness analyses will be performed based on demographics and baseline characteristics. However, if data for patients who have been treated with Pradaxa beyond the scope of approved label are collected, separate effectiveness analyses will be conducted.

7.3.2 Secondary analyses

There is no secondary effectiveness analysis planned in this study. However, additional exploratory analyses will be conducted as deemed appropriate.

7.3.3 Safety analyses

Demographic and baseline characteristics (including specifically stroke/bleeding risk scores ($CHADS_2$, CHA_2DS_2-VASc and HAS-BLED)) will be summarized descriptively for the entire cohort of eligible patients.

Adverse events (AEs) will be coded according to the latest version of Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding system. Concomitant therapies will be coded according to the latest version of KIMS (Korea Index of Medical Specialties) coding system. The trial database will not be locked until coding is complete.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Pradaxa. However, if data for patients who have been treated with Pradaxa beyond the scope of approved label are collected, separate safety analyses will be performed. Safety analyses will be performed based on demographics and baseline characteristics.

Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

7.3.4 Interim analyses

In accordance with local regulation for NIS studies, interim analyses are planned biannually for the initial two years and annually thereafter.

7.4 HANDLING OF MISSING DATA

As this is non-interventional study, there are no required investigations and diagnostic procedures (e.g. lab, ultrasound).
Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis. There will be no imputation of data to fill the missing values.

7.5. RANDOMISATION

This section is not applicable as this is a non-interventional study.

7.6 DETERMINATION OF SAMPLE SIZE

Sample size of 3,000 patients is based on the requirement of the local regulatory authority (Korean FDA). The number of patients enrolled for short-term surveillance will be 1,500 and for long-term follow up 1,500. As per regulation, long-term surveillance is necessary for the indication. It will be conducted to 50% of total number of enrolled patients.

8. DATA PROTECTION, STUDY RECORDS

The International Conference on Harmonization/Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP) does not often apply to NIS studies as most elements are relevant for controlled clinical trials. However, in this NIS study, all attempts will be made to adhere, as close as possible, to the standards of ICH/GCP.

The protocol of this regulatory requisite NIS study will be submitted to the Ministry of Food and Drug Safety (MFDS) for notification. It is not a local requirement in Korea to obtain Institutional Review Board (IRB) approval for the conduct of regulatory requisite NIS studies. However, the protocol of this NIS study will be submitted to IRBs whenever required or requested by these institutions. This study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

Boehringer Ingelheim Korea will submit periodic reports during re-examination period, and the final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC and the competent authority (CA) according to the local regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written data release consent shall be obtained from each patient (or the patient's legally accepted representative). Each signature must be personally dated by each signatory and the data release consent and any additional patient-information form retained by the NIS physician as part of the trial records. A signed copy of the data release consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

The patient shall be informed that his/her medical records may be examined by authorised monitors (NIS Managers) or Clinical Quality Assurance auditors appointed by sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the participating physician's study-related files and correspondence, and the data release agreement documentation of this study.

8.3 RECORDS

All of the clinical data will be captured via a web-based EDC (Electronic Data Capture) System. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The treating physician will approve the data using an electronic signature.
Patients will not be identified on the eCRF by name. Appropriate coded identification (i.e., patient number) will be used. The treating physician will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in this study in case follow-up is required. Likewise, any supporting documentation will be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents will be filed at the treating physician's site.

It is necessary that the data entered in the eCRFs that are transcribed from the source documents are consistent with the source documents or the discrepancies need to be explained. The treating physician may need to request previous medical records, transfer records, and current medical records.

8.3.2 Direct access to source data and documents

The NIS physician / site will permit study-related monitoring, audits and regulatory inspection, providing direct access to all related source data/documents. All source documents including eCRFs will be made available for review by sponsor's Medical Project Manager (MPM) or designees and inspection by health authorities (e.g., MFDS). The MPM and auditor may review all eCRFs, and written data release agreements. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

The NIS physician and the site are jointly responsible for maintaining essential study documents for 3 years after completion of the study (defined as termination date of re-examination period) by the Pharmaceutical Affairs Law and shall take measures to prevent accidental or premature destruction of these documents.

8.4 PROCEDURES FOR REPORTING ADVERSE EVENTS

8.4.1 Time windows

All AEs, serious and non-serious, occurring during the course of the rNIS will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRF. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the site materials (that include all necessary documents, the protocol, instructions for conducting rNIS, the package insert etc.).

The investigator has the responsibility to report AEs during the specified observational phase.

Any SAE, whether or not considered related to Pradaxa capsules, must be reported immediately via eCRF and SAE Report Form.

8.4.2 Documentation of adverse events and patient narratives

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to the local regulatory requirements.

For each AE, the investigator will provide the onset date, end date, intensity, outcome, seriousness and action taken with Pradaxa capsules. The investigator will determine the relationship of Pradaxa capsules to all AEs as defined in the 'Adverse Event Reporting' section of the protocol.

8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data will be made available to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated from the study will be made available for inspection on request by the participating physicians, the sponsor and/or its representatives and/or designees, by the IRBs/IECs and the regulatory authorities.

8.6 PUBLICATION POLICY

Boehringer Ingelheim, to the best of their ability will support the process of free exchange of relevant scientific information. Any publication of the result of this NIS study must be consistent with the Boehringer Ingelheim publication policy.

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10. APPENDICES

10.1 RISK SCORES FOR AF PATIENTS

Data collected at the baseline visit will be used to generate the following scores for use in the respective analysis:

Table 10.1: 1 $CHADS_2$ Stroke Risk Score

$CHADS_2$ component	**Points**
Congestive heart failure	1
Hypertension	1
Age greater than 75 years	1
Diabetes mellitus	1
Prior cerebral ischemia (i.e., stroke, TIA)	2
Maximum score	6

$CHADS_2$ score is based on a point system in which 2 points are assigned for the history of stroke or transient ischemic attack and 1 point each for age more than 75 years, hypertension, diabetes, or clinical heart failure or impaired left ventricular systolic function (generally interpreted as an ejection fraction $\leq 40\%$). A $CHADS_2$ score of 0 identifies patients at low stroke risk, a score of 1 to 2 identifies patients at moderate stroke risk, and a score greater than 2 identifies patients at high stroke risk (P06-10925).

Table 10.1: 2 CHA_2DS_2-VASc Stroke Risk Score

CHA_2DS_2-VASc Stroke score	
Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	**Clinically relevant non-major risk factors**
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40 %) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	9

* Myocardial infarction, complex aortic plaque and PAD

The CHA_2DS_2-VASc risk score is based on a point system in which 2 points are assigned for the history of stroke or TIA, or age ≥75; and 1 point each for age 65–74 years, hypertension, diabetes, cardiac failure, vascular disease and female sex. On the basis of the risk strata defined in previous guidelines, a CHA_2DS_2-VASc score of 0 corresponds to “low risk”, a score of 1 corresponds to “intermediate risk”, and a score of 2 or more corresponds to “high risk” (R10-5332).

Table 10.1: 3 HAS-BLED Bleeding Risk Score

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	**Clinical characteristics**	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum score		9

Hypertension is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA the value for 'labile INRs' will not be assessed.

A HAS-BLED score of ≥3 indicates 'high risk' for AF patients to develop a bleed and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin *(*R10-6394).

Table 10.1: 4 Modified Rankin Scale (mRS)

Definition of disabling stroke by modified Rankin Scale:

Grade 0: no symptoms at all

Grade 1: no significant disability despite symptoms;
able to carry out all usual duties and activities

Grade 2: slight disability:
unable to carry out all previous activities but able to look after own affairs without assistance

Grade 3: moderate disability
requiring some help but able to walk without assistance

Grade 4: moderate severe disability
unable to walk without assistance and unable to attend to own bodily needs without assistance

Grade 5: severe disability
bedridden, incontinent, and requiring constant nursing care and attention

Grade 6: dead

10.2 CREATININE CLEARANCE

The serum creatinine clearance will be calculated according to Cockroft-Gault:

Cl_{cr} (ml/min) = (140-age)*weight (kg) * GF

72 * Scr (mg/dL)

Clcr = Creatinine clearance

$S_{cr}Cr_s$ = Serum creatinine

(when serum creatinine is given in µmol/L, divide the value by 88.4)

GF = Gender correction factor (0.85 for women and 1.00 for men)

10.3 ELECTRONIC CASE REPORT FORM

See the Attachment 1.

10.4 SAE REPORT FORM

See the Attachment 2.

10.5 PREGNANCY MONITORING FORM

See the Attachment 3.

10.6 PRODUCT LOCAL LABEL

See the Attachment 4.

10.7 SPECIAL PRECAUTIONS FOR USE_RISK OF BLEEDING

See the Attachment 5.

11. SUMMARY OF NIS STUDY PROTOCOL MODIFICATIONS

Summary of Modifications Sheet (SOMS)

Number of Protocol modification		Amendment IV
Date of Protocol modification		11 Aug 2011 (Amendment I) 29 Nov 2012 (Amendment II) 18 Feb 2013 (Amendment III) 10 Jun 2013 (Amendment IV)
BI Trial number		1160.139
BI Product(s)		Dabigatran etexilate mesilate
Title of protocol		A regulatory requirement non-interventional study to monitor the safety and effectiveness of Pradaxa (Dabigatran etexilate mesilate, 110 mg or 150 mg b.i.d.) in Korean patients with non-valvular atrial fibrillation (SPARK: Safety study of Pradaxa in AF patients by Regulatory requirement of Korea)
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒ Mainly according to the revised local label of Pradaxa, the patient enrollment was changed.
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Please refer to the protocol amendment table_V4.0
Description of change		
Rationale for change		