Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c15727707-01**
BI Study Number:	1160.0284
BI Investigational Product(s):	Dabigatran etexilate
Title:	Post-Marketing Surveillance on the Use of Prazaxa® Capsules in Japanese patients with nonvalvular atrial fibrillation after the availability of idarucizumab
Brief lay title	Japanese Prazaxa PMS, second
Protocol version identifier:	Version 1.0
Date of last version of protocol:	Initial
PASS:	Yes
EU PAS register number:	NA
Active substance:	Dabigatran etexilate
Medicinal product:	Prazaxa® Capsules 75 mg 110 mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To confirm appropriate use and safety profile of Prazaxa® Capsules with prospective investigation in the routine medical practice after the availability of idarucizumab
Country(-ies) of study:	Japan
Author:	[redacted] (Trial Clinical Monitor, [redacted]

Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	22 February 2017

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
BI	Boehringer Ingelheim
CABG	Coronary Artery Bypass Graft
CML	Local Clinical Monitor
CrCL	Creatinine Clearance
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
GPSP	Good Post- marketing Study Practice
GVP	Good Pharmacovigilance Practices
IRB	Institutional Review Board
J-PAL	Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices
LAA	Left Atrial Appendage
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
[redacted]	
NIS	Non-Interventional Study
NVAF	Non-Valvular Atrial Fibrillation
PASS	Post-Authorization Safety Study
PCI	Percutaneous Coronary Intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Pharmaceuticals and Medical Devices
PMS	Post Marketing Surveillance
PSR	Periodic safety report
PT	Prothrombin Times
PT-INR	Prothrombin Time-International Normalized Ratio
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

3. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the PMS tracking system which manage the contracts with site and investigators name.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Protocol date: 22 February 2017	**Study number:** 1160.0284	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Title of study:	Post-Marketing Surveillance on the Long-Term Use of Prazaxa® Capsules in Japanese patients with nonvalvular atrial fibrillation after the availability of idarucizumab		
Rationale and background:	Even after the availability of idarucizumab in real clinical practice, appropriate use of Prazaxa® Capsules will continue. The patient population who receive Prazaxa® Capsules and the safety profile of Prazaxa® Capsules is not expected to change. This study can confirm appropriate use with prospective investigation in the routine medical practice.		
Research question and objectives:	The study objective is to confirm appropriate use and safety profile of Prazaxa® Capsules in real-world setting after the availability of idarucizumab.		
Study design:	Observational study based on newly collected data for 52 weeks.		
Population:	- Inclusion criteria Male and female patients with nonvalvular atrial fibrillation who have never received Prazaxa® Capsules / dabigatran etexilate for preventing the occurrence of ischemic stroke and systemic embolism before enrolment in Japan - Exclusion criteria None		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Protocol date: 22 February 2017	**Study number:** 1160.0284	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Variables:	Outcomes: Safety Primary outcomes: Incidences of adverse drug reactions [redacted] Others: baseline characteristics Demographics, duration and medical condition of indication, medical history/ concomitant disease, history of bleeding events, concomitant/ past medications and therapy, vital signs and safety laboratory tests, pregnancy		
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system		
Study size:	5000 (safety set)		
Data analysis:	Analyses are descriptive in nature, incidence rates and corresponding confidence intervals, absolute and relative frequencies will be given.		
Milestones:	Planned start of data collection: 1 JUL 2017 Planned end of data collection: 30 SEP 2020 Interim results will be submitted in the re-examination dossier to PMDA in APR 2019. Study Report planned to be archived in 3Q 2021 Study result based on study report is submitted additionally as a part of the re-examination dossier to PMDA in 4Q 2021.		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

6. MILESTONES

Milestone	Planned Date
Start of data collection	1 July 2017
End of data collection	30 September 2020
Study progress report	None
Study interim report 1	17 December 2017 (J-PSR)
Study interim report 2	17 December 2018 (J-PSR)
Study interim report 3	20 April 2019 (J-PSR)
Study interim report 4	20 April 2019 (re-examination dossier for Prazaxa Capsules)
Registration in the EU PASS register	To be registered
Final report of study results:	3Q 2021

7. RATIONALE AND BACKGROUND

This PMS study is planned additionally to the requirement by the Act on Pharmaceuticals and Medical Devices (PMD Act) in Japan. The regulatory required PMS (BI trial number: 1160.130) has been completed in January 2017.
The data collected in the PMS study are required to be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the local regulatory agency in Japan, according to the process of re-examination which will take place 8 years after approval of registration.

In Japan, idarucizumab (Prizbind®), a specific reversal agent of dabigatran, launched in November 2016, and the treatment environment of stroke prevention in patient with NVAF has changed. Even after the availability of idarucizumab in real clinical practice, the safety profile of dabigatran is not changed, and patients who recommend dabigatran also will not change. Also, appropriate use of dabigatran will continue as before.
Contraindication as per Japanese Package Insert should be respected.

However, we considered that the prospective investigation such as special drug use survey regarding the status of appropriate use of dabigatran under real clinical practice including whether idarucizumab influences to safety profile of dabigatran is necessary. Meanwhile, the previous regulatory required PMS (BI trial number: 1160.130) has already been completed, so it is unable to evaluate the influence on appropriate use of dabigatran under real clinical practice with the impact of idarucizumab launch as this rate. Therefore, we decided to conduct this newly planned PMS study (BI trial number: 1160.0284).
As for the survey items, evaluation points of this PMS study are consistent with previous regulatory required PMS because of taking into consideration descriptive differences.
With regard to the data obtained in this PMS study, we will provide interim analysis results to the clinical sites for the purpose of promoting further appropriate use of dabigatran.

8. RESEARCH QUESTION AND OBJECTIVES

The study objective is to confirm appropriate use and safety profile of Prazaxa® Capsules in real-world setting after the availability of idarucizumab.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational study based on newly collect real-world data (i.e., data under real-world practice) to confirm appropriate use and safety of Prazaxa® Capsules in real-world setting in patients with nonvalvular atrial fibrillation.

The study will consist of a baseline visit and further visits in a 52-week follow-up for patients who have initiated the Prazaxa® Capsules treatment.

9.2 SETTING

9.2.1 Study sites

Sites throughout entire country will be equally listed according the size of the hospitals or general clinics at which Prazaxa® Capsules are available for prescription.

Planned number of site: Approximately 800 Sites

A medical representative will explain the objective and design of this study to investigators at each study site and exchange a written contract with the head of the study site (e.g., hospital director).

9.2.2 Study population

As this is an observational study, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for nonvalvular atrial fibrillation must be according to regular medical practice and at discretion of physician (i.e., no randomised assignment of patient to treatment [Prazaxa® Capsules or other treatment] is performed).

Inclusion criteria

Male and female patients with nonvalvular atrial fibrillation who have never received Prazaxa® Capsules / dabigatran etexilate for preventing the occurrence of ischemic stroke and systemic embolism before enrolment in Japan

Exclusion criteria

None

9.2.3 Study visits

Registration periods: From July 2017 to June 2019

The registration method will be a continuous investigation system. Patients who begin treatment with Prazaxa® Capsules after the conclusion of the contract will be registered by entering necessary information in the EDC within 14 days whenever possible from the day of treatment initiation (inclusive).

Patient registration will be stopped when the target number of the study is reached. After the end of the registration period, investigators use a signed form to confirm that patients have been registered continuously at the site. A log of all patients included into the study will be maintained at the site.

After start of the treatment with Prazaxa® Capsules, each patient will be observed for 52 weeks or at premature discontinuation from the PMS. Observations are made at the following time points: before first administration of Prazaxa® Capsules (this visit is defined as baseline), 4, 8, 12, 26 and 52 weeks after the start of treatment, or at discontinuation.

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the PMS overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the PMS, or any other administrative reasons.
3. Violation of Good Post-marketing Study Practice (GPSP), the NIS protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the PMS

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

9.3 VARIABLES

9.3.1 Exposures

Exposure to Prazaxa® Capsules is estimated as time from the day Prazaxa® Capsules is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).

Patients newly initiating Prazaxa® Capsules will be followed up to 52 weeks.

9.3.2 Outcomes

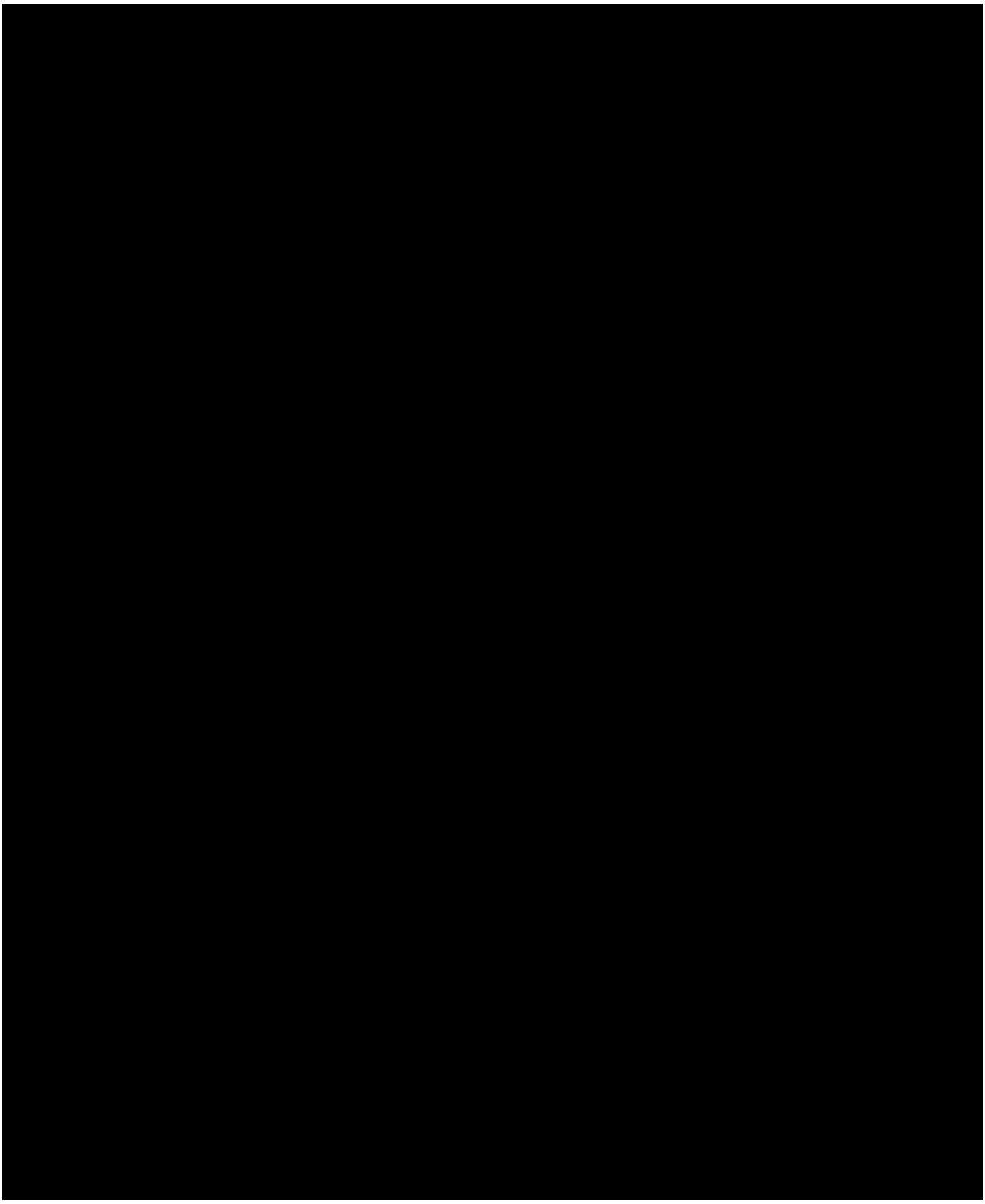
9.3.2.1 Primary outcomes

The primary Outcome is the absolute and relative (%) frequency of patients with suspected adverse drug reactions (ADRs).

There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

9.3.2.2 Secondary outcomes

None



9.3.3 Covariates

At least the following variables based on physician's report will be considered important baseline characteristics and potential risk factors for the outcomes of interest.

- gender, date of birth, indication, pregnancy status, patient status (inpatient/outpatient), body weight, height, hypersensitive disposition, alcohol status, smoking status
- atrial fibrillation (date of onset, disease type, electric cardioversion status, pharmacological cardioversion status, ablation treatment status, pace maker status, LAA occlusion status, LAA amputation status)
- concomitant disease/medical history (cardiac failure congestive, left ventricular hypertrophy, hypertension, diabetes mellitus, stroke, transient ischemic attack, systemic embolism, pulmonary embolism, deep-vein thrombosis, peripheral arterial disease, aortic plaque, thyrotoxicosis, hyperlipidemia, ischemic heart disease, myocardial infarction, valvular disease, hepatic function disorder, renal impairment [including CrCL and eGFR if applicable], gastro intestinal disorder, cancer, dementia and others)
- history of bleeding events

- antithrombogenic drugs administered before the day of first administration of Prazaxa® Capsules
- concomitant / past medications and therapy
- Administration of Prazaxa® Capsules (dose, daily frequency, in the first administration-reason to prescribe lower dose (other than 150mg bid), start and end date, primary reason of discontinuation, use of idarucizumab)
- blood pressure and pulse rate (if applicable)
- laboratory tests (blood biochemistry and urinalysis) (if applicable)
  Haematology: Leukocyte count (WBC), Haemoglobin (Hb), Erythrocyte count (RBC), Platelet count, Haematocrit

  Blood chemistry: AST (aspartate transaminase, SGOT), ALT (alanine transaminase, SGPT), γ-GTP (gamma-glutamyl-transferase), Total bilirubin (T-BIL), Total cholesterol (T-CHO), HDL cholesterol (HDL), LDL cholesterol (LDL), Triglycerides (TG), Fasting blood glucose, HbA1c, Blood urea nitrogen (BUN), Creatinine (CRE), Uric acid (UA), Sodium (Na), Potassium (K), Chlorine (Cl), Alkaline Phosphatase (Al-P)

  Urinalysis: Protein, Glucose, Urobilinogen, Uric blood

  Blood coagulation test: aPTT, PT-INR, PT (baseline only)

  To calculate eCCR, the Cockcroft-Gault formula will be used.

$$\text{eCCR} = \frac{(140-\text{AGE})\times \text{WT[kg]}}{72\times \text{SCR [mg/dL]}} \times 0.85 (\text{if female})$$

  To calculate eGFR, the following formula will be used.

$$\text{eGFR} = 194 \times \text{SCR}^{1.094} \times \text{AGE}^{-0.287} \times 0.739 \text{ (if female)}$$

  WT: body weight, SCR: serum creatinine

  See ANNEX 2 for more details.

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the Electronic Data Capture (EDC) system.

In EDC system, two casebooks will be set up.:
Book 1 includes baseline, 4 weeks, 8 weeks and 12 weeks.
Book 2 includes 26 weeks and 52 weeks.

The data are to be transmitted immediately after being entered into EDC at 12 weeks (Book 1) and 52 weeks (Book 2) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9.5 STUDY SIZE

In order to consider with the PMS study (1160.130) (December 2011-March 2016) in descriptive manner after obtaining the results from this PMS, sample size of this survey is planned as same as the study 1160.130 for the patients with nonvalvular atrial fibrillation. From the interim results (cut-off date: 17 September 2016) of PMS 1160.130, the rate of major bleeding event was 0.37 per 100 patient-year (30/6443, 95%CI: 0.26-0.53). However, since follow-up duration is reduced by half compared with 1160.130. This might lead to a decreased precision in the estimation of outcome incidence rates.

9.6 DATA MANAGEMENT

Patients' data will be gathered by EDC system provided by external vendor below.

	Contract 1	Contract 2
Company Name	To be determined.	[redacted]
Outsourced work	EDC system setting Patient registration Clinical Data Management	Document management of contract with site.

9.7 DATA ANALYSIS

This is an observational study to collect real-world data (i.e., data under routine medical practice) on safety and appropriate use of Prazaxa® Capsules treatment. Analyses are descriptive in nature, including confidence intervals. Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study. Subgroup analyses are also performed if sample size allows.

Per local regulation, any patient who meets one of the following criteria is treated as ineligible for all analyses:

- No safety observation was documented after registration.
- No required registration procedure was followed.
- No valid site contract was available.

9.7.1 Main analysis

The analysis of outcome events will include all patients registered in the study and receiving the Prazaxa® Capsules treatment. All outcome events are based on reported AE data which will be handled according to BI standards.
The safety analysis will include all patients registered in the study and receiving the Prazaxa® Capsules treatment except for patients who meet the ineligible criteria (see section 9.7). In general, safety analyses will be descriptive in nature, be based on BI standards, and focus on AEs related to the Prazaxa® Capsules treatment.

AEs will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between the initiation of Prazaxa® Capsules prescribed at baseline visit and 6 days (inclusive) after the last administration will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician/investigator who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The incidence (n and % in treatment group) and treatment exposure time adjusted incidence rate (n in 100 patient years) of AEs in patients treated with Prazaxa® Capsules (treatment emergent including 6 days after discontinuation of Prazaxa® Capsules medication) will be tabulated by MedDRA SOC and PT for overall and for subgroups based on the important baseline characteristics, if sample size allows.

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

The safety data will be assessed by using demographic data (e.g. indication for use, CrCL) in terms of appropriate use.

[redacted]

9.7.3 Interim analyses

Several interim analyseswill be performed for the purpose of submission of periodic safety reports to PMDA in project (status update of using Prazaxa® Capsules not only with this trial but all usage, every 6 month in two years after approval and every 12 months afterward. The submission date is depending on the time from the approval).

Interim results will be submitted in the re-examination dossier to PMDA by 20 April 2019.

9.8 QUALITY CONTROL

All processes are conducted according to GPSP SOPs and GPSP working instruction. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of the adverse events in the population under study. Due to the nature of a single cohort observational study, however, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up, channeling bias and information and recall bias. Thus, comparisons and causal conclusions cannot be made, except for the investigator reported drug-related AEs.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

This PMS is to be conducted in accordance with both the in-house SOP and working instructions which are in compliance with GPSP.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via Electronic Data Capture (EDC) system.

9.10.2.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents for PMS study is not allowed in Japan.

9.10.3 Completion of study

Completion of the PMS will be notified to PMDA when the re-examination document is applied to in accordance with J-PAL and GPSP.

10. PROTECTION OF HUMAN SUBJECTS

There is no regulation or requirement for ensuring the well-being and rights of participants in a non-interventional observational study.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by IRB is not mandatory for conducting PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (e.g., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.2 STATEMENT OF CONFIDENTIALITY

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

Data generated as a result of the PMS needs to be available for inspection on request by the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions (see 001-MCS-05-501-RD-01 for collection requirements) and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

11.1 DEFINITIONS OF ADVERSE EVENTS

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

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

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

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or

development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An AE which possibly leads to disability will be reported as an SAE.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

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

The following must be collected by the investigator in the eCRF. When any adverse events occur, the data should be immediately entered into eCRF and transmitted.:

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

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

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

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

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

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

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

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

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

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

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

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

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

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than Prazaxa® Capsules, according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report

forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted to PMDA in Japan PSR (Periodic safety report). And also the interim report for this PMS is included in re-examination documents.
This study is planned for the publication based on the final report.

The rights of the physician and of the sponsor with regard to publication of the results of this PMS are described in the contract. As a general rule, no PMS results should be published prior to finalisation of the Study Report.

In addition, further interim analysis might be performed for the scientific presentations and publications for the purposes of promoting appropriate use of Prazaxa® Capsules.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R11-1250 Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202-4.

P11-05406 Lip GYH, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P, Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis.
Europace 13, 723 - 746 (2011)

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None	None		

ANNEX 2. FLOW CHART OF VARIABLES

Time point / Item	Observation period [*1]					
	Before first administration of Prazaxa® Capsules	Week 4	Week 8	Week 12	Week 26	Week 52 or at discontinuation
Patient enrolment	X[*2]					
Surveillance items:						
• Patient demographic	X					
• Atrial fibrillation characteristics	X					
• Concomitant disease/ medical history	X					
• History of bleeding events	X					
• Prior Anti-thrombotic therapy	X					
• Administration status of Prazaxa® Capsules		X (Record throughout the observation period)				
• Concomitant drug / Concomitant therapy		X (Record throughout the observation period)				
• Blood pressure/pulse rate	(X)	(X)	(X)	(X)	(X)	(X)
• Pregnancy status	X (confirm throughout the observation period)				X (confirm throughout the observation period)	
• Laboratory tests[*3]	(X)	(X)	(X)	(X)	(X)	(X)
• Stroke/SEE, Haemorrhage, myocardial infarction and gastrointestinal disorder		X (Examine throughout the observation period)				
• Adverse events		X (Examine throughout the observation period)				

*1: Time points during the observation period are approximate. Collected data should be reported as of the closest available visit.

*2: Patients administered Prazaxa® Capsules will be registered within 14 days from whenever the day of first administration is possible.

*3: All aPTT and PT-INR data measured at any time during the observation period should be completely entered into eCRF.

(X): If applicable

eCRF (electronic case report form): At 12 weeks, 52 weeks, and each time an adverse event has occurred, data in corresponding observation period should be entered into the eCRF and transmitted using the EDC system.

APPROVAL / SIGNATURE PAGE

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