# Non-Interventional Study (NIS) Protocol

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| **Document Number:** | **c32188789-01** |
| **BI Study Number:** | 1160-0304 |
| **BI Investigational Product(s):** | Dabigatran (Pradaxa®) |
| **Title:** | Relationship of Advanced Holding Education and ADherence on antithrombotic in younger NVAF patients |
| **Brief lay title:** | ReAHEAD |
| **Protocol version identifier:** | Version 1.0 |
| **Date of last version of protocol:** | NA |
| **PASS:** | No |
| **EU PAS register number:** | Study not registered. |
| **Active substance:** | Dabigatran etexilate mesylate (ATC code: B01AE07) |
| **Medicinal product:** | Dabigatran |
| **Product reference:** | TFDA number: 026233 (75 mg), 025459 (110 mg), 025458 (150 mg) |
| **Procedure number:** | EMA agency product number: EMEA/H/C/000829 |
| **Marketing authorisation holder(s):** | This study is initiated, managed, and financed by: [redacted] |
| **Joint PASS:** | No |
| **Research question and objectives:** | The primary objective of this study is to explore whether the advanced educational intervention would improve the adherence to dabigatran, in a 12-month follow-up period for newly diagnosed atrial fibrillation (AF) adult patients under 75 years old.<br><br>The secondary objectives are to describe comorbidities and [redacted] VASc score at baseline and at the end of the study; and to describe stroke, thromboembolic events, and bleeding events in dabigatran |

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| | patients (with or without advanced educational intervention) in a 12-month follow-up period for AF adult patients under 75 years old. |
| **Country(-ies) of study:** | Taiwan |
| **Author:** | [redacted]<br>Title: [redacted]<br>Name: [redacted]<br>Tel: [redacted]<br>Mobile: [redacted]<br>Fax: [redacted]<br>Email: [redacted] |
| **Marketing authorisation holder(s):** | [redacted]<br>Title: [redacted]<br>Name: [redacted]<br>Tel: [redacted]<br>Mobile: [redacted]<br>Fax: [redacted]<br>Address: [redacted]<br>Email: [redacted] |
| *In case of PASS, add:* **MAH contact person:** | Not applicable |
| *In case of PASS, add:* **<EU-QPPV:>** | Not applicable |
| *In case of PASS, add:* **<Signature of EU-QPPV:>** | Not applicable |
| **Date:** | 21-Oct-2020 |



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# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AESI | Adverse Event of Special interest |
| AF | Atrial Fibrillation |
| ALP | ALkaline Phosphatase |
| ALT | ALanine aminoTransferase |
| AST | ASpartate aminoTransferase |
| BI | Boehringer Ingelheim |
| CA | Competent Authority |
| Ccr | Creatinine clearance rate |
| CrCl | Creatinine Clearance |
| CI | Confidence Interval |
| CML | Clinical Monitor Local |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DMP | Data Management Plan |
| DVP | Data Validation Plan |
| eCRF | Electronic Case Report Form |
| eGFR | estimated Glomerular Filtration Rate |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| GCP | Good Clinical Practice |
| GEP | Good Epidemiological Practice |
| GPP | Good Pharmacoepidemiology Practice |
| GVP | Good Pharmacovigilance Practices |
| Hb | Hemoglobin |
| IEC | Independent Ethics Committee |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| MAH | Marketing Authorisation Holder |
| MMAS-8 | Morisky 8-Item Medication Adherence Questionnaire |
| NHIRD | National Health Insurance Research Database |
| NIS | Non-Interventional Study |
| NOAC | New Oral AntiCoagulants |
| NSAID | NonSteroidal Anti-Inflammatory Drug |
| NVAF | Non-Valvular Atrial Fibrillation |
| OAC | Oral AntiCoagulant |
| PASS | Post-Authorization Safety Study |
| PT | Prothrombin Time |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |

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| TFDA | Taiwan Food and Drug Administration |

# 3. RESPONSIBLE PARTIES

| Title | Name |
|---|---|
| [redacted] | |
| [redacted] of Medical Affairs | [redacted] |
| Medical Advisor | |
| Medical Science Liaison | |
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| Project [redacted] | |
| Medical Affairs/Assistant [redacted] | |
| Regulatory Affairs/Assistant [redacted] | |
| Data [redacted] /Biostatistician [redacted] | |
| Clinical Research [redacted] | |

# 4. ABSTRACT

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|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Dabigatran (Pradaxa®) | | | |
| **Name of active ingredient:** Dabigatran etexilate mesylate (ATC code: B01AE07) | | | |
| **Protocol date:** 21-Oct-2020 | **Study number:** 1160-0304 | **Version/Revision:** Version 1.0 | **Version/Revision date:** NA |
| **Title of study:** | Relationship of Advanced Holding Education and ADherence on antithrombotic in younger NVAF patients | | |
| **Rationale and background:** | The overall prevalence of atrial fibrillation (AF) in Taiwanese was 1.4% in men and 0.7% in women in 2008 and is estimated to be 4.01% in 2050. Patients with AF face a strongly elevated risk of stroke—about 3- to 5-fold higher after adjustment for risk factors.<br><br>Adherence<br><br>Lifelong oral anticoagulant (OAC) therapy is the preferred treatment for the prevention of thromboembolic events in the majority of patients with AF. Adherence to medication is essential for valid treatment for OAC therapy. Non-adherent patients (proportion of days covered for new oral anticoagulants [NOAC] is < 80%) were reported to be 2.08 times more likely to experience the ischemic stroke compared to the adherent patients in one year. | | |

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| | A retrospective study from the USA of evaluating the adherence rate of OACs by Morisky 8-Item Medication Adherence Questionnaire (MMAS-8) score concluded that the adherence could be attributed to differences in health knowledge and duration taking anticoagulant medication. Age is another influencing factor of the treatment adherence. Younger patients have significantly worse adherence compared to older ones because of their low awareness of risks of AF and benefits of AF treatments regarding the prevention of ischemic events. Patients under 75 years old might have lower risk scores but their poor adherence may increase the incidence of stroke and lifetime economic burden (e.g., work loss and premature death). Providing advanced education material to patients who are under 75 years old to increase their awareness of the importance of early intervention and drug adherence may be a feasible strategy to enhance the adherence rate to OACs among younger patients, to reduce stroke/or recurrent risk, and to contribute to socioeconomic saving. However, such health education has not been implemented in Taiwan currently.<br><br>Therefore, we would like to initiate a non-interventional study (NIS) in newly diagnosed AF adult patients who are under 75 years old and are prescribed with dabigatran. The study aims to explore whether the advanced educational intervention would improve the adherence to dabigatran.<br><br><u>Epidemiology</u><br><br>The risk of ischemic stroke in AF is heterogeneous, depending on different risk factors with age being the important driver of stroke risk. The optimal assessment should include age and incident comorbidities. In addition, different comorbidities should be identified due to the different relative contributions to stroke. However, preliminary Taiwanese data are limited especially for data from newly diagnosed AF patients. In parallel to treatment adherence, we would like to collect the routine clinical practice data on occurrence of comorbidities in newly diagnosed AF patients prescribed with dabigatran. | | |
| **Research question and objectives:** | The primary objective of this study is to explore whether the advanced educational intervention would improve the adherence to dabigatran, in a 12-month follow-up period for newly diagnosed atrial fibrillation (AF) adult patients under 75 years old.<br><br>The secondary objectives are to describe comorbidities and [redacted]VASc score at baseline and at the end of the study; and to describe stroke, thromboembolic events, and bleeding events in dabigatran patients in a 12-month follow-up period for AF adult patients under 75 years old. | | |

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| **Study design:** | This is a multi-center, 1:1 randomized study to evaluate the effects of educational intervention on adherence to dabigatran, for up to 12 months. Adult patients newly diagnosed with AF within 1 month, under 75 years old, and newly prescribed with dabigatran on physician's decision per local labelling will be equally randomized to receive standard of care (routine clinical practice) or standard of care (routine clinical practice) with advanced educational intervention.<br><br>The study duration consists of a 1-year enrolment period and a 12-month follow-up period consisting of visits at 3, 6, 9, and 12 months. Being an NIS, the time points of follow-up visits are set in accordance with the routine outpatient follow-ups of AF in Taiwan.<br><br>The educational materials from "Shared decision making of treatment of NOAC in AF patients" (NTA: 180647) and "Atrial Fibrillation Patient Care in Hospitals" (NTA: 190707) will be used as the educational materials for the experimental group. The education material will be delivered after randomization (baseline); and at 3, 6, and 9 months thereafter. The adherence to dabigatran will be measured by MMAS-8 score at 3, 6, 9, and 12 months.<br><br>The comorbidities, [redacted]VASc scores, and HAS-BLED scores will be recorded at baseline; and 3, 6, 9, and 12 months. Stroke, thromboembolic events, and bleeding-related events will also be captured during 12 months. |
| **Population:** | <u>Inclusion criteria</u><br><br>Patients can be included if ALL the following criteria are met:<br><br>(1) Provide written informed consent prior to participation<br><br>(2) Female or male patients aged ≥ 20 years and < 75 years, newly diagnosed with non-valvular atrial fibrillation (NVAF) within 1 month and has newly prescribed with dabigatran on physician' s decision before study enrolment.<br><br><u>Exclusion criteria</u><br><br>Patients should not be included if ANY ONE of the following criteria is met:<br><br>(1) Contraindication to the use of dabigatran (i.e., active pathological bleeding, history of a serious hypersensitivity reaction to dabigatran [e.g., anaphylactic reaction or anaphylactic shock], severely impaired renal function [Ccr < 30 mL/min], hemorrhagic manifestations, bleeding diathesis, mechanical prosthetic heart valve, congenital or acquired coagulation disorders, organic lesions with bleeding tendency, or concomitantly use systemic ketoconazole, cyclosporine, and itraconazole) |

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| | (2) Participate in other interventional trials currently or in the past 30 days | | |
| **Variables:** | Baseline characteristics<br>▪ Demographics (date of birth, gender, race, etc.)<br>▪ AF-related medical histories<br>▪ [redacted] VASc score<br>▪ HAS-BLED score (modified HAS-BLED for newly initiated patients)<br>▪ Kidney function (creatinine clearance [CrCl] and estimated glomerular filtration rate [eGFR])<br>▪ Comorbidities<br>▪ Concomitant therapies related to bleedings and AF<br>▪ Dosing of dabigatran<br>Primary outcome<br>The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 12 months in patients with and without advanced educational intervention<br>Secondary outcomes<br>(1) The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 3, 6, and 9 months in patients with and without advanced educational intervention<br>(2) The proportion of patients with medium (MMAS-8 score: 6 – 7 points) and low (MMAS-8 score < 6 points) adherence to dabigatran treatment at 3, 6, 9, and 12 months in patients with and without advanced educational intervention<br>(3) The mean MMAS-8 score at 3, 6, 9, and 12 months in patients with and without advanced educational intervention<br>(4) The discontinuation rate of dabigatran and reasons for discontinuation (switch or stop treating dabigatran) in patients with and without advanced educational intervention<br>Further outcomes<br>Among pooled patient set (dabigatran patients with and without advanced educational intervention) following outcomes are presented | | |

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| | (1) To describe the [redacted] VASc score at baseline and at the end of study visit<br>(2) To describe newly identified risk factors (including hypertension, diabetes, congestive heart failure, vascular disease [myocardial infarction, peripheral artery disease, and complex aortic plaque], ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia) at baseline and at the end of the study<br>(3) Stroke and thromboembolic events during the 12-month follow-up<br>(4) Bleeding-related events during the 12-month follow-up<br>(5) HAS-BLED score at baseline and the end of study<br>(6) Other ADRs | | |
| **Data sources:** | As this is an NIS, data will be captured through the MMAS-8 questionnaires and medical charts at approximately 20 hospitals (20 ± 3) where dabigatran 110 mg and/or 150 mg are listed in hospital formulary for NVAF treatment. A case report form (CRF) will be designed to collect the variables of interests. | | |
| **Study size:** | Approximately 1,200 patients from around 20 hospitals (20 ± 3) will be enrolled in this study. Assuming a drop-out rate of 20%, it is expected to have 1,000 patients completing the study. The sample size is determined based on the feasibility, planned enrolment period, number of potential patients at selected sites, and expected precision of the estimates. As the selected sites are the hospitals with most AF patients treated with dabigatran in Taiwan from northern to southern areas, the patients recruited into this study will be the representative of the AF population treated with dabigatran and the healthcare settings in Taiwan. | | |
| **Data analysis:** | A data management plan (DMP) and statistical analysis plan (SAP) will be prepared to describe all processes, variables, and specifications for data collection, cleaning, validation, and analyses.<br>The analyses will be mainly descriptive. All patients who have signed the informed consent and fulfilled study criteria will be included in the main analysis. | | |

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| | Continuous variables will be reported as number, mean, standard deviation (SD), minimum, maximum, and 95% confidence interval (CI). Categorical variables will be summarized as number and frequency or percentage with observed (non-missing) data.<br><br>Analysis of endpoints:<br><br>▪ The primary outcome is to describe the proportion of patients with high adherence to dabigatran treatment which is defined as achieving MMAS-8 score of 8 points at 12 months for each group. Subjects without MMAS-8 value recorded at 12 months will be excluded from the analysis of primary endpoint.<br>▪ Mean MMAS scores at 3, 6, 9, and 12 months will be compared between patients with and without advanced educational intervention using Chi-square, Fisher's exact, or other appropriate tests for categorical data and using t-test or Wilcoxon rank-sum test for continuous data. Similarly, subjects without MMAS-8 value recorded at a specific visit will be excluded from the analysis of corresponding secondary endpoints.<br>▪ Other secondary outcomes in patients with and without advanced educational intervention separately and further outcomes only within pooled patient set (e.g., comorbidities, stroke/thromboembolic/bleeding events, risk factors, ADR, etc.) will all be analyzed in a descriptive manner.<br>▪ All tests will be done under a statistical level of 0.05.<br><br>Imputation of missing data will be permitted, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SAP. All statistical assessments will be performed using Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC, USA). | | |
| **Milestones:** | Planned start of data collection: Sep 2020<br>Planned end of data collection: Sep 2022<br>Planned final study report: Feb 2023 | | |

# 5. AMENDMENTS AND UPDATES

None.

# 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| First IRB/IEC approval | July 2020 |
| First site contract signed | Aug 2020 |
| Start of data collection | Sep 2020 |
| Enrolment completed | Sep 2021 |
| End of data collection | Sep 2022 |
| Database lock | Dec 2022 |
| Final report of study results: | Feb 2023 |

# 7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and it is a global problem.[1] The overall prevalence of atrial fibrillation (AF) in Taiwanese was 1.4% in men and 0.7% in women in 2008[2] and is estimated to be 4.01% in 2050.[3] Patients with AF face a strongly elevated risk of stroke—about 3- to 5-fold higher after adjustment for risk factors.[4] According to an analysis of AF patients without treating any antiplatelet or oral anticoagulant (OAC) from the National Health Insurance Research Database (NHIRD; 1996 – 2011) of the whole Taiwanese population, the event rate of ischemic stroke in AF patients with [redacted] VASc score from 0 to 7 points was increasing from 1.1 to 13.33 per 100 person-years.[5]

Treatment adherence

Lifelong OAC therapy is the preferred treatment for the prevention of thromboembolic events in the majority of patients with AF. Adherence to medication is essential for valid treatment for OAC therapy.[6] Non-adherent patients (proportion of days covered for new oral anticoagulants [NOAC] is < 80%) were reported to be 2.08 times more likely to experience the ischemic stroke compared to the adherent patients in one year.[7] A retrospective study from the USA of evaluating the adherence rate of OACs by Morisky 8-Item Medication Adherence Questionnaire (MMAS-8) score found a high adherence (MMAS-8 score reaches 8) rate of 71% to dabigatran and concluded that the adherence could be attributed to differences in health knowledge and duration taking anticoagulant medication.[8]

Age is another influencing factor of adherence. Younger patients have significantly worse adherence compared to older ones[9] because of their low awareness of risks of AF and benefits of AF treatments regarding the prevention of ischemic events. Patients under 75 years old might have lower risk scores but their poor adherence may increase the incidence of stroke and the lifetime economic burden (e.g., work loss and premature death).[10,11] Providing advanced education to patients who are under 75 years old to increase their awareness of the importance of early intervention and drug adherence may be a feasible strategy to enhance the adherence rate to OACs among younger patients, to reduce stroke/or recurrent risk, and to contribute to socioeconomic saving. However, such health education has not been implemented in Taiwan currently.

Therefore, we would like to initiate a non-interventional study (NIS) in newly diagnosed AF adult patients who are under 75 years old and are prescribed with dabigatran. The study aims to explore whether the advanced educational intervention would improve the adherence to dabigatran.

Epidemiology

The risk of ischemic stroke in AF is heterogeneous, depending on different risk factors with age being as an important driver of stroke risk. Age thresholds for the use of NOACs are different for AF patients having different risk factors beyond sex despite the threshold of [redacted] VASc score point is the same (1 point for males and 2 points for females); that is, 35 years for heart failure, 50 years for hypertension or diabetes, and 55 years for vascular disease.[12] The data support that the optimal assessment should include age and incident comorbidities. In addition, different comorbidities should be identified due to the different relative contributions to stroke. However, preliminary Taiwanese data are limited especially for data from newly diagnosed AF patients. In parallel to this NIS, we would like to collect real-world data to examine the occurrence of comorbidities in newly diagnosed AF patients prescribed with dabigatran.

# 8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to explore whether the advanced educational intervention would improve the adherence to dabigatran, in a 12-month follow-up period for newly diagnosed atrial fibrillation (AF) adult patients under 75 years old.

The secondary objectives are to describe comorbidities and [redacted] VASc score at baseline and at the end of the study; and to describe stroke, thromboembolic events, and bleeding events in dabigatran patients in a 12-month follow-up period for AF adult patients under 75 years old.

# 9. RESEARCH METHODS

## 9.1 STUDY DESIGN

This is a multi-center, 1:1 randomized study to evaluate the effects of educational intervention on adherence to dabigatran, for up to 12 months. The study will be carried out at around 20 hospitals (20 ± 3), where AF patients are mainly treated in Taiwan. A total of 1,200 patients are planned to be enrolled to target 1,000 patients included in the analysis.

Patients newly diagnosed with AF within 1 month, under 75 years old, and newly prescribed with dabigatran on physician's decision per local labelling will be enrolled and equally randomized to receive standard of care (routine clinical practice) or standard of care (routine clinical practice) with advanced educational intervention. To create the randomization numbers, we will use block randomization by Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC, USA).

The study duration consists of a 1-year enrolment period and a 12-month follow-up period consisting of visits at 3, 6, 9, and 12 months for each individual patient. Being an NIS, the time points of follow-up visits are set in accordance with the routine outpatient follow-ups of AF management in Taiwan. Patients will be continuously followed until death, lost to follow-up, or end of data collection at 12 months, whichever comes first.

The educational materials from "Shared decision making of treatment of NOAC in AF patients" (NTA: 180647) and "Atrial Fibrillation Patient Care in Hospitals" (NTA: 190707) will be used as the educational materials for the experimental group. The education materials will be delivered after randomization (baseline); and at 3, 6, and 9 months thereafter. The adherence to dabigatran will be measured by MMAS-8 score at 3, 6, 9, and 12 months.

The comorbidities, [redacted] VASc score, and HAS-BLED score will be recorded at baseline; and at 3, 6, 9, and 12 months. Stroke, thromboembolic events, and bleeding-related events will also be captured during 12 months of follow-up.

The whole NIS will be implemented by a Contract Research Organization (CRO) under Local Boehringer Ingelheim's governance.

## 9.2 SETTING

The study is planned to be carried out at around 20 hospitals (20 ± 3), where AF patients are mainly treated in Taiwan. A total of 1,200 patients will be enrolled to have 1,000 patients included in the analysis.

### 9.2.1 Study sites

Selected sites include around 20 hospitals (20 ± 3) (mostly are major medical centers) in Taiwan, from Northern to Southern area, with physicians, facilities, and adequate clinical data that reflect the locally clinical practice. The site selection criteria will help to ensure that the patients recruited into this study will be the representative of the AF population treated with dabigatran and the healthcare settings in Taiwan.

### 9.2.2 Study population

Potential patients will be screened in accordance with the study criteria in Section 9.2.2.1 and 9.2.2.2. Only patients who meet all study criteria will be enrolled and randomized into study groups.

A subject screening log should be kept at the site, recording basic information (e.g., initials, gender, date of birth, and reasons for not enrolling the patient) on all patients who are invited to participate in the study, with the information on the eligibility (or reasons for non-eligibility) and date of signed informed consent. In addition, a log of all patients included into the study (i.e., having given informed consent) will be maintained in the study file at the study site.

#### 9.2.2.1 Inclusion criteria

Patients can be included if ALL the following criteria are met:

(1) Provide written informed consent prior to participation

(2) Female or male adult patients aged ≥ 20 years and < 75 years, newly diagnosed with non-valvular atrial fibrillation (NVAF) within 1 month and has newly prescribed with dabigatran on physician' s decision before study enrolment.

#### 9.2.2.2 Exclusion criteria

Patients should not be included if ANY ONE of the following criteria is met:

(1) Contraindication to the use of dabigatran (i.e., active pathological bleeding, history of a serious hypersensitivity reaction to dabigatran [e.g., anaphylactic reaction or anaphylactic shock], severely impaired renal function [Ccr < 30 mL/min], hemorrhagic manifestations, bleeding diathesis, mechanical prosthetic heart valve, congenital or acquired coagulation disorders, organic lesions with bleeding tendency, or concomitantly use systemic ketoconazole, cyclosporine, and itraconazole)

(2) Participate in other interventional trials currently or in the past 30 days

#### 9.2.2.3 Withdrawal criteria

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her well-being. If a patient ends the study earlier, the physician must record the discontinuation/withdrawal reason on the

CRF. A patient may discontinue the study participation due to any one of the following reasons:

(1) Withdrawal of consent

(2) Lost to follow-up

(3) Administrative problems

(4) Death

### 9.2.3 Study visits

The collection of patient data will be managed in line with routine clinical practice in an outpatient manner, which will have follow-ups at approximately every 3 months in Taiwan. Information on variables of interest will be collected at inclusion (baseline visit) and captured during the follow-up period at 3, 6, 9, and 12 months (time window: ± 6 weeks) until completion of the study.

Data will be collected and recorded on the CRF according to Table 1 which lists all of the data of interests with an "X" to show the time points when they are collected. Data will be collected after the patient has consented to participate in the study. Once the patient has signed the informed consent form, the patient is considered to be enrolled in the study and patient details should be recorded on the enrolment log.

Table 1 Data collection schedule

| **Event** | **Screening/Baseline** | **Follow-up** | | | |
|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** |
| **Month** | **0** | **3** | **6** | **9** | **12** |
| **Week** | **0** | **12** | **24** | **36** | **48** |
| Allowed window | -- | ± 6 weeks | | | |
| Informed consent | X | | | | |
| Inclusion/exclusion | X | | | | |
| Randomization | X | | | | |
| Demographics[1] | X | W/A | W/A | W/A | W/A |
| AF-related medical histories[2] | X | | | | |
| Comorbidities | X[3] | X[4] | X[4] | X[4] | X[4] |
| Serum creatinine (for CrCl) and eGFR[5] | X | X | X | X | X |
| [redacted]VASc score | X | X | X | X | X |
| HAS-BLED score | X | X | X | X | X |
| Lab data for HAS-BLED[6] | X | X | X | X | X |
| Concomitant therapies for HAS-BLED[7] | X | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| Education (experimental group) | X | X | X | X | |
| Dabigatran treatment | X | X | X | X | X |
| Concomitant therapies for AF or stroke[8] | X | X | X | X | X |
| MMAS-8 score | | X | X | X | X |
| Stroke and thromboembolic events[9] | → | | | | |
| Bleeding-related events[10] | → | | | | |
| Safety reporting[11] | → | | | | |

1. Demographics include date of birth, gender, race, education level, height, weight, and alcoholic status (defined as ≥ 8 units [1 unit = approximately 355-mL beer, 150-mL wine, 20-mL Kaoliang] of consumption per week). Follow-up visits will only collect weight (W) and alcoholic status (A).
2. Include date of AF diagnosis and type of AF (paroxysmal, persistent or permanent).
3. At baseline, comorbidities will be recorded as follows according to the medical records:
   - Currently ongoing diseases: Hypertension, diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
   - Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque) ischemic heart disease, stroke, transient ischemic attack, and thromboembolism
4. At follow-up visits, only the current and newly onset of comorbidities since the last visit should be recorded. Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia
5. CrCl will be calculated using Cockcroft-Gault formula.
   - For baseline, the most updated results prior to the enrolment will be collected.
   - For follow-up visits, data within the allowed window and closest to the visit will be collected.
6. Lab data include liver function tests (bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) and coagulation tests

(international normalized ratio [INR] and prothrombin time [PT]. For baseline, the most updated results prior to the enrolment will be collected.

- For follow-up visits, data within the allowed window and closest to the visit will be collected.

7. Concomitant therapies are chronic dialysis or renal transplant due to abnormal renal function & medication usage predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs [NSAIDs]).
   - For baseline, chronic dialysis or renal transplant prior to baseline will be collected, while medication usage predisposing to bleeding within 1 month prior to baseline will be collected.
   - For follow-up visits, concomitant therapies used during the interval of visits will be collected.
8. Concomitant therapies for AF or stroke prevention within 1 month prior to the enrolment will be collected at baseline.

   Changes in concomitant therapies will be collected at follow-up visits.
9. Events include but not limited to stroke, myocardial infarction, peripheral arterial occlusion, pulmonary embolism, venous thrombosis, transient ischemic attack, and thromboembolism.
10. Events include but not limited to intracranial, gastrointestinal, intraspinal, intraocular, pericardial, intra-articular, intramuscular, perioperative, retroperitoneal, and genitourinary bleeding.
11. Dabigatran relevant adverse drug reaction (ADR, serious and non-serious), fatal adverse events (AEs), and pregnancies.

#### 9.2.3.1 Screening/Baseline (Visit 1)

The following procedures will be performed at the baseline visit. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Collect signed informed consent form. A copy of the signed consent should be given to the patient.
- Assess the eligibility according to the inclusion/exclusion criteria and record the date of inclusion
- Randomize the eligible patients into one of the study groups (standard of care OR standard of care with advanced educational intervention)
- Collect demographic data (date of birth, gender, race, education level, height, weight, and alcoholic status [defined as ≥ 8 units of consumption per week])
- Record AF-related medical histories
- Record the following comorbidities:
  - Currently ongoing diseases: Hypertension, diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal

transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

- Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, stroke, transient ischemic attack, and thromboembolism

- Collect the latest results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR prior to the baseline
- To acquire HAS-BLED score:
  - Record the latest results of bilirubin, AST, ALT, ALP, INR, and PT prior to the baseline
  - Record if the subject is receiving chronic dialysis or had undergone renal transplant due to abnormal renal function prior to the baseline; and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) within 1 month prior to the baseline
- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the concomitant therapies for AF or stroke prevention within 1 month prior to the baseline (generic name or name of the therapy)
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

Information to be collected from screen failure individuals

The screening log entry with demographic information and the primary reason for not continuing or ineligibility must be completed for all screened patients that do not qualify for study entry. No CRF other than the screening log will be collected from these patients. The subject number of ineligible patients should be kept. The following enrolments will be numbered in sequence.

#### 9.2.3.2 Month 3 ± 6 weeks (Visit 2)

The following procedures will be performed at 3 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since the baseline (during baseline to Month 3). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque),

ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 3 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 3 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during baseline to 3 months
- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention after baseline (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

#### 9.2.3.3 Month 6 ± 6 weeks (Visit 3)

The following procedures will be performed at 6 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since Visit 2 (during Month 3 to Month 6). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 6 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 6 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 3 to 6 months
- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

#### 9.2.3.4 Month 9 ± 6 weeks (Visit 4)

The following procedures will be performed at 9 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since Visit 3 (during Month 6 to Month 9). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 9 months will be collected.
- To acquire HAS-BLED score:

- Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 9 months will be collected.
- Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 6 to 9 months

- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

#### 9.2.3.5 Month 12 ± 6 weeks (Visit 5)

The following procedures will be performed at 12 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since the visit 4 (during Month 9 to Month 12). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 12 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR and PT if available in medical record. Only the values within the allowed window and closest to 12 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 9 to 12 months

- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

### 9.2.4 Study discontinuation

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

(1) Failure to meet expected enrolment goals overall or at a particular study site

(2) Emergence of any efficacy/safety information that could significantly affect the continuation of the study, or any other administrative reasons.

(3) Violation of Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), or Good Pharmacoepidemiology Practice (GPP) (as applicable), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

## 9.3 VARIABLES

### 9.3.1 Exposures

Being an NIS, the prescription of dabigatran will be in accordance with the Summary of Product characteristics and physician's discretion. Treatment record of dabigatran will be collected and recorded on CRF across the 12 months of study period. Data to be collected include start/end date of administration, dose, and the reason for dose adjustment or interruption.

### 9.3.2 Outcomes

9.3.2.1 Primary outcomes

The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 12 months in patients with and without advanced educational intervention

9.3.2.2 Secondary outcomes

(1) The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 3, 6, and 9 months in patients with and without advanced educational intervention

(2) The proportion of patients with medium (MMAS-8 score: 6 – 7 points) and low (MMAS-8 score < 6 points) adherence to dabigatran treatment at 3, 6, 9, and 12 months in patients with and without advanced educational intervention

(3) The mean MMAS-8 score at 3, 6, 9, and 12 months in patients with and without advanced educational intervention

(4) The discontinuation rate of dabigatran and reasons for discontinuation (switch or stop treating dabigatran) in patients with and without advanced educational intervention

[redacted]

9.3.2.4 Morisky 8-Item Medication Adherence Questionnaire (MMAS-8)

The MMAS-8 is an 8-item structured, self-report measure that assesses medication adherence.[13] It has been proved to be a valuable resource to address adherence concerns, such as forgetting to take medications or discontinuing medications without guidance.[14] If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with non-adherence.

The validated Chinese MMAS-8 will be used to evaluate the adherence to dabigatran at baseline and every follow-up visit. Patients are considered to have low adherence with scores less than 6, medium adherence with scores of 6 to 7, and high adherence with a score of 8.

9.3.2.5 Stroke and thromboembolic events

Stroke and thromboembolic events to be captured include but not limited to stroke, myocardial infarction, peripheral arterial occlusion, pulmonary embolism, venous thrombosis, transient ischemic attack, and thromboembolism.

Investigators and study staffs should check if patients experience above events across the 12 months of follow-up. Whenever a stroke and thromboembolic event happens, the investigator should judge its severity (mild, moderate, or severe) and record the event on the CRF.

9.3.2.6 Bleeding-related events

Bleeding-related events to be captured include but not limited to intracranial, gastrointestinal, intraspinal, intraocular, pericardial, intra-articular, intramuscular, perioperative, retroperitoneal, and genitourinary bleeding.

Bleeding-related events will be further classified into "Major bleeding" or "Minor bleeding" based on the following definitions:

- Major bleeding: Bleeding that is fatal, symptomatic in critical area or organ (intracranial, life-threatening, or requiring surgery), causing hemoglobin (Hb) fall of ≥ 2.0 g/L or leading to transfusion of ≥ 2 units.
- Minor bleeding: Bleeding not meeting the criteria for major bleeding but requiring medical intervention, change in antithrombotic therapy, or considered clinical relevant by the physician.

Investigators and study staffs should check if patients experience above events across the 12 months of follow-up. Whenever a bleeding-related event happens, the investigator should judge its severity (mild, moderate, or severe) and record the event on the CRF.

### 9.3.3 Covariates

Patients recruited will be evaluated for covariates at the visit of baseline. Potential confounders include demographics (age, gender, race, and educational level), [redacted] VASc score, HAS-BLED score, comorbidities, concomitant therapies, dose of dabigatran, and renal function.
If any covariate or confounding/interacting variable that may possibly influence the outcome is noted, additional analyses may be carried out to identify its effect. Details of handling covariates will be given in the statistical analysis plan (SAP), if any covariate of interest is detected.

9.3.3.1 Baseline characteristics

- Demographics (date of birth, gender, race, educational level, height, weight, and alcoholic status [defined as ≥ 8 units of consumption per week])

- AF-related medical histories (date of AF diagnosis and type of AF [paroxysmal, persistent or permanent])
- Kidney function (CrCl and eGFR)

Value of serum creatinine within the allowed window (i.e., the latest data before baseline & data within ± 6 weeks for follow-up visits) will be collected from medical chart to calculate the CrCl value by Cockcroft-Gault formula as below.[15,16]

When serum creatinine is measured in mg/dL, the value is multiplied by a constant of 0.85 if the patient is female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

(1) When serum creatinine is measured in µmol/L, constant is 1.23 for male and 1.04 for female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

- [redacted]VASc score (Section 9.3.3.4)
- HAS-BLED score (Section 9.3.3.5)
- Comorbidities (Section 9.3.3.2)
- Concomitant therapies for AF or stroke prevention: Generic name or name of the therapy

### 9.3.3.2 Comorbidities

Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

At baseline, comorbidities will be recorded as follows according to the medical records:

- Currently ongoing diseases: Hypertension; diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

- Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque) ischemic heart disease, stroke, transient ischemic attack, thromboembolism

At follow-up visits, only the current and newly onset of comorbidities since the last visit (regardless of its condition, resolved or unresolved) should be recorded on the CRF.

#### 9.3.3.3 Concomitant therapy

The study will collect two types of concomitant therapies, including (1) therapies related to the calculation of HAS-BLED score and (2) therapies for AF or stroke prevention. These therapies will be collected according to the plan as below:

(1) Therapies related to HAS-BLED score include chronic dialysis or renal transplant due to abnormal renal function & medication usage predisposing to bleeding (antiplatelet agents or NSAIDs).

- Baseline: Chronic dialysis or renal transplant prior to baseline will be collected, while medication usage predisposing to bleeding within 1 month prior to baseline will be collected.
- Follow-up visits at every 3 months: Used during the interval of visits will be collected

(2) Therapies for AF or stroke prevention:

- Baseline: Used within 1 month prior to the enrolment will be collected at baseline.
- Follow-up visits at every 3 months: Changes in concomitant therapies will be collected.

#### 9.3.3.4 [redacted] VASc score

The [redacted] VASc score[17] is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF. The [redacted] VASc score is composed of eight items with a maximum score of 9. Among all the items, two of them have extra weight of 2 points, including “age 75 and above” and “stroke, transient ischemic attack, and thromboembolism”; while the other six items are counted as 1 point of each. A higher score corresponds to a greater risk of stroke. The [redacted] VASc score is calculated according to Table 2.

Table 2 Acronym [redacted] VASc and the score

| Letter | Clinical Characteristic | Score |
|---|---|---|
| [redacted] | | |

| | | |
|---|---|---|
| V | Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) | 1 |
| A | Age 65 – 74 years | 1 |
| Sc | Sex category (i.e., female sex) | 1 |

#### 9.3.3.5 HAS-BLED score

HAS-BLED[18] is a scoring system developed to assess 1-year risk of major bleeding in patients with AF. The HAS-BLED score is composed of seven items with a maximum score of 9. Among all the items, 2 of them will be scored with 1 or 2 points depending on the number of corresponded description, including "abnormal renal and liver function" and "drugs or alcohol", while the other five items are counted as 1 point of each. A higher score corresponds to a greater risk of bleeding, and a score of ≥ 3 points indicates "high risk". The HAS-BLED score will be calculated according to Table 3.

Table 3 Clinical characteristics composing the HAS-BLED score

| Letter | Clinical Characteristic | Score |
|---|---|---|
| H | Hypertension[1] | 1 |
| A | Abnormal renal function[2] and abnormal liver function[3] (1 point each) | 1 or 2 |
| S | Stroke[4] | 1 |
| B | Bleeding[5] | 1 |
| L | Labile INRs[6] | 1 |
| E | Elderly, age > 65 years | 1 |
| D | Drugs or alcohol (1 point each)[7] | 1 or 2 |

1. Hypertension should be uncontrolled, with systolic blood pressure > 160 mmHg.
2. Abnormal kidney function is classified as a presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 μmol/L.
3. Abnormal liver function is defined as the chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal, and so forth.)
4. Previous history, particularly lacunar.
5. Bleeding history, such as prior major bleeding or predisposition to bleeding (e.g., anemia).
6. Labile INR (e.g., therapeutic time in range < 60%).
7. Drugs are medication usage predisposing to bleeding (e.g. antiplatelet agents or NSAIDs). Ethanol abuse is classified as ≥ 8 units of alcoholic consumption per week.

## 9.4 DATA SOURCES

As this is an NIS, no diagnostic or monitoring procedures additional to the standard of care and routine practice (except for the additional education delivered to the experimental group) will be applied to the patients. All the assessment will be performed by the investigator if they are deemed necessary for the medical treatment procedure.

This study will collect the data from medical charts and MMAS-8 questionnaires. Investigators or delegated site staffs will record the data on the CRF. Data source includes questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, etc.

## 9.5 STUDY SIZE

Approximately 1,200 patients from around 20 hospitals (20 ± 3) will be enrolled in this study. Assuming a drop-out rate of 20%, it is expected to have 1,000 patients completing the study. The sample size is determined based on the feasibility, planned enrolment period, number of potential patients at selected sites, and expected precision of the estimates. As the selected sites are the hospitals with most AF patients treated with dabigatran in Taiwan from northern to southern areas, the patients recruited into this study will be the representative of the AF population treated with dabigatran and the healthcare settings in Taiwan.

## 9.6 DATA MANAGEMENT

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

Designated CRO will serve as the statistical and data coordinating center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

The data from enrolling patients in this study will be recorded on a CRF or other applicable forms. The designated CRO will capture, check, store, and analyze the data. The designated CRO will follow Boehringer Ingelheim standard operating procedures (SOPs) and their own internal SOPs.

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning, and validation. Validation process will be performed as outlined in a data validation plan (DVP). Queries will be reviewed and sent to the study investigators for clarification. Designated site staffs for investigation are required to reply the queries and make any necessary changes to the data. The queries will be resolved and data will be updates under the agreement of investigator. Once all queries have been resolved, the database will be locked. The locked data will be exported to generate the subject listings, tabulations, and statistical analyses.

Data will be transferred to Boehringer Ingelheim after the closure of the study.

## 9.7 DATA ANALYSIS

Analyses will be performed by a designated CRO. The main analysis population will consist of all eligible patients (i.e., all patients who have signed the informed consent and fulfilled all inclusion criteria and no exclusion criteria).

Analytic specifications, including tables and listings, will be detailed in the statistical analysis plan (SAP) that is separate from the full study protocol. A change to the data analysis methods described in the study protocol will require an amendment only if it changes a principal feature of the study objective. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All statistical assessments will be performed using Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC, USA).

### 9.7.1 Main analysis

The analyses will be mainly descriptive to gain an understanding of the characteristics of the sample studied.

Continuous variables will be reported as number, mean, standard deviation (SD), minimum, maximum, and 95% confidence interval (CI). Categorical variables will be summarized as number and frequency or percentage with observed (non-missing) data.

Analysis of endpoints:

- The primary outcome is to describe the proportion of patients with high adherence to dabigatran treatment which is defined as achieving MMAS-8 score of 8 points at 12 months for each group. Subjects without MMAS-8 value recorded at 12 months will be excluded from the analysis of primary endpoint.
- The Mean MMAS scores at 3, 6, 9 and 12 months will be compared between patients with and without advanced educational intervention using Chi-square, Fisher's exact, or other appropriate tests for categorical data and using t-test or Wilcoxon rank-sum test for continuous data. Similarly, subjects without MMAS-8 value recorded at a specific visit will be excluded from the analysis of corresponding secondary endpoints.
- Other secondary outcomes in patients with and without advanced educational intervention separately and further outcomes only within pooled patient set (e.g., comorbidities, stroke/ thromboembolic/ bleeding events, risk factors, ADR, etc.) will all be analyzed in a descriptive manner
- All tests will be done under a statistical level of 0.05.

[redacted]

### 9.7.3 Handling of missing data

For withdrawals, the information already collected as part of the study data will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

Imputation of missing data will be permitted, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SAP. In addition, if the proportion of patients of whom the MMAS-8 score at 12 months is missing or cannot be calculated is substantial (e.g. ≥ 10%), baseline characteristics will be described for patients whose MMAS-8 score at 12 months is missing in comparison to patients who have completed 12-month follow-up.

## 9.8 QUALITY CONTROL

Before the study launch, participating physicians will be trained on the protocol, safety reporting (Section 11) and study conduct procedures by Boehringer Ingelheim (or designee).

In keeping with the non-interventional design employed in this study, site interaction (e.g., direct contact between site study staff or patients and representatives of the call center or the study coordinating center) is minimized.

Source data verification will be performed for critical study outcomes in this study. At any time during the course of the study, the site study staff may contact designated personnel for clarification of the study conduct. All information will be kept confidential.

During the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the clinical database has been declared to be complete and accurate, it will be locked.

To ensure the data accuracy, completeness, and reliability, quality control will be the ongoing, concurrent review of data collection forms for completion and logic. The research staffs will preserve documented data from all sources on the CRF, including lab test results, chart records, treatment conditions, physical examination, concomitant medication, and any safety information.

Boehringer Ingelheim or designated CRO will assure database quality processes are followed including the review of the data entered into the CRFs by investigational staffs for completeness and accuracy, and in accordance with the DVP.

## 9.9 LIMITATIONS OF THE RESEARCH METHODS

An NIS is the most suitable design for obtaining information about the use of medicines in everyday therapeutic practice and thus for clarifying prospectively questions in everyday therapeutic practice. In addition, the observational design intends to collect available data that are recorded on medical charts. The lack of data of interest may be one of the limitations.

All efforts will be made to minimize missing data and loss to follow-up in patients who are enrolled. For instance, before start of data collection, a study initiation visit will be performed for each site, where investigators and site staffs will be trained for study implementation, data

collection, and safety reporting. Investigators and site staffs should escalate issues that can potentially jeopardize study outcomes to sponsor or CRO upon awareness. Sponsor, CRO, and site should work closely to manage any risks.

The entry criteria are non-restrictive and will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator. Selection bias could occur at both the site (physician) level and the patient level. To minimize the site level selection bias, the goal is to have participating centers (i.e., medical centers of Taiwan) that are representative of the management of AF patients in Taiwan and have access to all available treatment options for AF that are approved for use in Taiwan.

Selection bias at the patient level could occur if sites preferentially enroll specific patients into the study. To minimize selection bias at the patient level, consecutive enrolment within 1 year will be enforced.

## 9.10 OTHER ASPECTS

No other aspect of the research method is not covered in the previous sections.

### 9.10.1 Data quality assurance

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

### 9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via paper. All paper CRFs should be typed or filled out with a black ball-point pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be signed and dated by the investigator or a member of the study staff authorized by the investigator on the Authority Form. No erasers, correction fluid, or tape can be used.
- The principal investigator will sign and put on the signature date on the CRFs. These signatures will indicate that the principal investigator has inspected or reviewed the data on the CRF, the data queries, and the site notifications; and has agreed with the content.

#### 9.10.2.1 Source documents

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These documents include but not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, MMAS-8

questionnaires, and correspondence. CRF records may be considered as source data if the CRF is the original recording (i.e., there is no any other written or electronic record of data).

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 in a locked cabinet.

Data reported on the CRFs 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; also, current medical records must be available.

For paper CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth, etc.)
- Patient participation in the study (substance, study number, patient number, the date when the patient consents the participation)
- Dates of patient's visits, including prescription of dabigatran and date of assessment
- Medical history or clinical diagnosis (including concomitant diseases and concomitant therapies)
- ADRs related to dabigatran and outcome events (i.e., stroke, thromboembolic events, bleeding-related events)
- Originals or copies of laboratory results or examinations
- Conclusion of patient's participation in the study
- Other study-specific variables

The physician must keep the original informed consent form signed by the patient (a signed copy must be given to the patient).

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on CRFs will be included on the authority form.

No information in source documents about the identity of the patients will be disclosed. No study document can be destroyed without prior written agreement between Boehringer Ingelheim and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Boehringer Ingelheim in advance.

#### 9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes, copies of laboratory, and medical test results, must be available at all times for review by the sponsor's clinical study monitor, auditor, and inspection by health authorities (e.g., Taiwan Food and Drug Administration [TFDA]). The Clinical Research Associate (CRA)/Clinical Monitor Local (CML) and the auditor may review

all CRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

# 10. PROTECTION OF HUMAN SUBJECTS

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

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

The rights of the investigator and of Boehringer Ingelheim with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the study report.

Insurance Cover: The requirements for insurance depend on local law and legislations. If required, the terms and conditions of the insurance cover are made available to the investigator and the patients, and the documentation must be archived in the investigator site file (ISF).

## 10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient. Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed of the study to the extent of his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. The process of obtaining informed consent should be documented in the patient source documents.

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

### 10.2 STATEMENT OF CONFIDENTIALITY

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

No subject names will be supplied to Boehringer Ingelheim or other responsible parties. Only the subject number and subject initials will be recorded on the CRF. If the subject's name appears on any other documents (e.g., laboratory report), it must be obliterated before a copy of the document is supplied to Boehringer Ingelheim or other responsible parties. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Treatment records may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, Boehringer Ingelheim's representatives, IRB/IEC, or regulatory authorities. All personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

### 11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable 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 drug reaction
An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or

- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

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

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

Adverse Event of Special Interest (AESI)

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs are defined for this study.

## 11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

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

The following must be collected by the investigator in the CRF from signing the informed consent onwards until the end of the study:

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

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

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

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

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

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

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction happening at 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 NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

The following must be reported on the NIS AE Form and/or Pregnancy Monitoring Form for Studies in case such AE/drug exposure during pregnancy information is identified in the course of the review of the individual records:

| | |
|---|---|
| All **serious ADRs** associated with Pradaxa® | immediately within 24 hours |

| | |
|---|---|
| All **AEs with fatal outcome** in patients exposed to Pradaxa® | immediately within 24 hours |
| All **non-serious ADRs** associated with Pradaxa® | 7 calendar days |
| Drug exposure during pregnancy in patients exposed to Pradaxa® | 7 calendar days |

The same timelines apply if follow-up information becomes available for the respective events.

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

The following must be collected by the investigator in the CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reactions (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.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provide o BI unique entry point:

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

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

Information required

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

Reporting of related Adverse Events associated with any other Boehringer Ingelheim drugs

The investigator is encouraged to report all adverse events related to any BI drug other than dabigatran 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 occurs 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 Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

## 13. REFERENCES

### 13.1 PUBLISHED REFERENCES

[1] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129 (8): 837-847.

[2] Chien K-L, Su T-C, Hsu H-C, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. International journal of cardiology. 2008;139 173-180.

[3] Chao TF, Liu CJ, Tuan TC, et al. Lifetime Risks, Projected Numbers, and Adverse Outcomes in Asian Patients With Atrial Fibrillation: A Report From the Taiwan Nationwide AF Cohort Study. Chest. 2018;153 (2): 453-466.

[4] Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28 (10): 973-977.

[5] Chao TF, Liu CJ, Wang KL, et al. Using the [redacted] VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. J Am Coll Cardiol. 2014;64 (16): 1658-1665.
[6] Kneeland PP, Fang MC. Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. Patient preference and adherence. 2010;4 51-60.
[7] Deshpande CG, Kogut S, Laforge R, Willey C. Impact of medication adherence on risk of ischemic stroke, major bleeding and deep vein thrombosis in atrial fibrillation patients using novel oral anticoagulants. Curr Med Res Opin. 2018;34 (7): 1285-1292.
[8] Patel SI, Cherington C, Scherber R, et al. Assessment of Patient Adherence to Direct Oral Anticoagulant vs Warfarin Therapy. J Am Osteopath Assoc. 2017;117 (1): 7-15.
[9] Harper P, Pollock D, Stephens M. Dabigatran persistence and adherence in New Zealand: a nationwide retrospective observational study. BMJ Open. 2018;8 (4): e020212.
[10] Kang HY, Lim SJ, Suh HS, Liew D. Estimating the lifetime economic burden of stroke according to the age of onset in South Korea: a cost of illness study. BMC Public Health. 2011;11 646.
[11] Smajlović D. Strokes in young adults: epidemiology and prevention. Vascular health and risk management. 2015;11 157-164.
[12] Chao TF, Lip GYH, Lin YJ, et al. Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: insights into the optimal assessment of age and incident comorbidities. Eur Heart J. 2019;40 (19): 1504-1514.
[13] Morisky Widget Software.
[14] Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. Journal of clinical hypertension (Greenwich, Conn). 2008;10 (5): 348-354.
[15] Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16 (1): 31-41.
[16] Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. Nephron. 1992;62 (3): 249-256.
[17] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137 (2): 263-272.
[18] Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138 (5): 1093-1100.

## 13.2 UNPUBLISHED REFERENCES

None.

# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | ReAHEAD-MMAS8-V1 | 12May2020 | Morisky 8-Item Medication Adherence Questionnaire |

# ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html is included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

"Study start" means "Start of data collection"
"Study progress" means "Progress report(s)"
"Study completion" means "End of data collection"
"Reporting" means "Final report of the study results"

# ANNEX 3. ADDITIONAL INFORMATION

None.