Boehringer Ingelheim

# Protocol for non-interventional studies based on existing data

| | |
|---|---|
| **Document Number:** | C17002710-01 |
| **BI Study Number:** | 1160.0288 |
| **BI Investigational Product(s):** | Prazaxa (Dabigatran etexilate) |
| **Title:** | Comparative Effectiveness and Safety between Warfarin and Dabigatran Using Real World Claims Data of Japanese Non-valvular Atrial Fibrillation Patients |
| **Protocol version identifier:** | version 1.0 |
| **Date of last version of protocol:** | Not Applicable |
| **PASS:** | No |
| **EU PAS register number:** | Not Applicable |
| **Active substance:** | Dabigatran and warfarin |
| **Medicinal product:** | Dabigatran and warfarin |
| **Product reference:** | Not applicable |
| **Procedure number:** | Not Applicable |
| **Joint PASS:** | No |
| **Research question and objectives:** | To compare the effectiveness (stroke/SE) (primary outcome) and safety (major bleeding) (secondary outcome) in patients with atrial fibrillation and newly treated with dabigatran and warfarin in the real world Japanese setting using a claims database |
| **Country(-ies) of study:** | Japan |
| **Author:** | [redacted] |
| **Marketing authorisation holder(s):** | [redacted] |

| | |
|---|---|
| **MAH contact person:** | [redacted] |
| *In case of PASS, add:* **<EU-QPPV:>** | Not Applicable |
| *In case of PASS, add:* <**Signature of EU-QPPV:>** | Not Applicable |
| **Date:** | 6 Jul 2017 |

# 1. TABLE OF CONTENTS

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AF | Atrial Fibrillation |
| AIC | Akaike Information Criterion |
| $CHADS_2$ | Congestive heart failure, Hypertension, Age, Diabetes, Stroke(doubled) |
| $CHA_2DS_2$-VASc | Cardiac failure or dysfunction, Hypertension, Age 75 (doubled), Diabetes, Stroke (doubled) Vascular disease, Age 65-74 and Sex category (female) score |
| CHF | Congestive Heart Failure |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Lung Disease |
| CT | Computed Tomography |
| DM | Diabetes Mellitus |
| DPC | Diagnosis Procedure Combination |
| HR | Hazard Ratio |
| ICD | International Classification of Diseases |
| ICH | Intracranial Hemorrhage |
| MDV | Medical Data Vision |
| MRI | Magnetic Resonance Imaging |
| NVAF | Non-Valvular Atrial Fibrillation |
| OAC | Oral Anticoagulants |
| PPV | Positive Predictive Value |
| PS | Propensity Score |
| PVD | Peripheral Vascular Disease |
| RR | Relative Risk |
| SD | Standard Deviation |
| SE | Systemic Embolism |
| [redacted] | [redacted] |

# 3. RESPONSIBLE PARTIES

Person responsible for trial

[redacted]

Data manager and analyser

[redacted]

Medical writing and claims coding

[redacted]

Data Source Provider:
Medical Data Vision Co., Ltd. (MDV)

# 4. ABSTRACT

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>Prazaxa | | | |
| **Name of active ingredient:**<br>Dabigatran etexilate | | | |
| **Protocol date:**<br>6 Jul 2017 | **Study number:**<br>1160.0288 | **Version/Revision:**<br>Version 1.0 | **Version/Revision date:**<br>Not applicable |
| **Title of study:** | Comparative Effectiveness and Safety between Warfarin and Dabigatran Using Real World Claims data of Japanese Non-valvular Atrial Fibrillation Patients | | |
| **Rationale and background:** | Real-world data about the characteristics of patients with NVAF initiating an oral anticoagulant (OAC) in Japan has been scarce to date. The purpose of this study is to compare the effectiveness and safety of dabigatran and warfarin using the MDV database. | | |
| **Research question and objectives:** | To compare the effectiveness (stroke/SE) and safety (major bleeding) in patients with atrial fibrillation and newly treated with dabigatran and warfarin in the real world Japanese setting using a claims database | | |
| **Study design:** | A non-interventional study based on existing health insurance claims data | | |
| **Population:** | Medical Data Vision (MDV) clinical database is used.<br>OAC-naïve, adult patients with NVAF initiating dabigatran or warfarin between 14 March 2011 (considering the launch date of dabigatran) and 30 June 2016 will be enrolled.<br>Inclusion criteria: patients aged >18 year-old with confirmed diagnosis of NVAF (ICD 10 code I48), having a first prescription (index date) of either dabigatran or warfarin between 14 March 2011 to 30 June 2016, having no prescription of any OACs for 12 months prior to the index date (this period is defined as the baseline period).<br>Exclusion criteria: patients having less than 12 months of enrolment prior to the index date, being dialysis or kidney transplant recipients in baseline period, having either atrial flutter, valvular AF, mechanical valve placement, rheumatic AF, and/or mitral valve prolapse/regurge/stenosis in baseline period, and having record of deep vein thrombosis or pulmonary embolism < 6 months before AF diagnosis in baseline period. | | |
| **Variables:** | Baseline characteristics of patients (age, sex, clinical history), year of initiating treatment, medical history, type of OAC and its dosage, concomitant medications, events related to stroke, systemic embolism, major bleeding, TIA, and myocardial infarction. | | |
| **Data sources:** | MDV clinical database. The database is health insurance claims database. As of end of February 2016, MDV provides commercial | | |

| | | | |
|---|---|---|---|
| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Prazaxa | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Protocol date:** 6 Jul 2017 | **Study number:** 1160.0288 | **Version/Revision:** Version 1.0 | **Version/Revision date:** Not applicable |
| | claims for in and out-patients consisting of medical records from more than 12.94 million patients from 230 large acute care DPC hospitals. .<br>Observation period is planned from 14 March 2010 to 30 June 2016 considering the launch date of dabigatran. | | |
| **Study size:** | The previous study 1160.279 was a feasibility study to look into the treatment pattern of OACs in Japan and internal validity of MDV database including availability of co-variates to conduct 1:1 PS matching. For warfarin and dabigatran comparison, the number of AF patients meeting inclusion and exclusion criteria after matching was 4,427 in each cohort. | | |
| **Data analysis:** | This study plans no formal hypothesis testing. The planned analyses are descriptive in nature and results are to be interpreted in an exploratory manner.<br>1:1 Propensity score matching (PSM) was conducted to to address potential channelling bias. Outcomes will be assessed in the PSM sample.<br>Patient characteristics prior to and after propensity score matching will be described stratified by treatment group.<br>Patients will be followed up from treatment initiation (index date) to the day of treatment discontinuation (defined as a treatment gap longer than 14 days past the number of days of supply of the last prescription), the day before a switch to a different anticoagulant, the date of disenrollment in MDV, the end of the study period, the occurrence of the event of interest, or death of the patient, whichever occurs first (as-treated analysis).<br>Number of observed events, number of patient years, the corresponding incidence rates and their 95% confidence intervals (CIs) will be reported.<br>Dabigatran and warfarin outcomes will be compared by estimating the hazard ratios (HRs) for the outcomes and their CIs using Cox regression.<br>Kaplan-Meier curves for event-free survival will be estimated. | | |
| **Milestones:** | Start of Data Analysis: 1 July 2017<br>End of Data Analysis: 07 July 2017<br>Study Report: 18 August 2017 | | |

# 5. AMENDMENTS AND UPDATES

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| | None | | | |
| | | | | |
| | | | | |

# 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Start of data analysis | 18 July 2017 |
| End of data analysis | 21 July 2017 |
| Final report of study results: | 18 Aug 2017 |

# 7. RATIONALE AND BACKGROUND

Until 2002 in Japan, administrative claims data were not standardized or coded electronically. There was limited use for Health Authorities policy decision making or in health research (epidemiological, HTA). Ministry of Health, Labor and Welfare launched the Diagnosis Procedure Combination (DPC) system in 2002 linked with the reimbursement system. DPC is a Japanese version of the Diagnosis Related Groups system; such system is implemented in many countries including UK, US and Germany.

The DPC is a case-mix system, similar to Medicare in the US. It comprises of 18 Major Diagnosis Categories, 520 diagnostic groups and 2,658 case-mix groups. In the DPC algorithm, the diagnosis, procedure and comorbidities/complications are the 3 key variables for classification.
The diagnosis and comorbidities/complications are coded using the International Classification of Diseases (ICD) 10 scheme, while the procedures are coded using the Japanese Procedure Codes. Not only administrative claims data but also detailed patient data are collected for all the inpatients discharged from the participating hospitals.Dabigatran, first of the novel oral anticoagulants (OACs) to be approved and launched in Mar 2011 in Japan, was supported by the findings from the RE-LY study, which showed dabigatran efficacy in stroke reduction compared to warfarin with 150mg (relative risk (RR)=0.65, 95% CI = 0.52-0.81) and 110mg dose group (RR=0.90, 95% CI 0.74-1.10).[1] Major bleeding was also found to be reduced in the RE-LY study for both dose groups (110mg RR = 0.80, 95% CI 0.70-0.93), 150mg RR = 0.93, 95% CI = 0.81-1.07) compared to warfarin.
Several real world evidence studies have been published recently to compare effectiveness and safety of dabigatran, rivaroxaban and apixaban using claims database from the U.S., Danish and Taiwan national claims databases.[2-5] In addition, several validation studies have been reported using DPC hospital claims database. Yamaguchi et al assessed the positive predictive value (PPV) of MDV claims defined event definitions for deep vein thrombosis, pulmonary embolism and bleeding events against clinical diagnosis of a panel of experts who examined claims codes and reached a consensus.[6] Although sample of events were relatively small (50 for each event) PPV for thromboembolic events was 75% and bleeding events was 73.3%. Yamana et al evaluated the DPC data identified Charlson co-morbid conditions from 4 mid-size acute care hospitals against chart review diagnosis for the validity of claims defined diagnosis.[7] Specificity was found to be over 96%, although sensitivity was below 50%. PPV for cerebrovascular disease diagnosis was reported to be 86.4% with negative predictive value of 93.5%. Koretsune et al conducted a validation study on MDV database to calculate the PPV for stroke, systemic embolism (SE) and intracranial hemorrhage (ICH) utilizing methodology similar to that reported by Yamaguchi et al, and found the PPV of stroke, SE events (SEE) and ICH to be 74%, 26.7% and 85.0%.[8] Second evaluation of SEE after changing claims definition increased the PPV to 86.7%.
There has been no comparative effectiveness or safety analysis of dabigatran vs. warfarin has been published using large scale Japanese claims database thus far.

# 8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to compare the effectiveness (incidence of stroke/SE) in Japanese patients with atrial fibrillation and newly treated with either dabigatran or warfarin.

The secondary objective is to compare safety (incidence of major bleeding) in patients with atrial fibrillation and newly treated with dabigatran and warfarin in the real world Japanese setting using a claims database.

[redacted]

# 9. RESEARCH METHODS

## 9.1 STUDY DESIGN

Study design
- Non-interventional new user cohort study based on existing data (Medical Data Vision (MDV) database) using propensity score matching

Treatments Considered:
- Dabigatran and warfarin

Strength of the study design
- Channelling bias as well as differences in baseline risk of outcome occurrence between treatment groups will be adressed by the use of propensity score (PS) matching

Outcomes
- Primary outcome: stroke and systemic embolism
- Secondary outcome: major bleeding defined by any bleeding event associated with hospitalization claims and/or transfusion claims
- [redacted]

## 9.2 SETTING

MDV clinical database is used.

Definition
1. Index date: the date of first oral anticoagulant prescription, namely warfarin or dabigatran
2. Baseline period: 12 months prior to and including the index date
3. Drug exposure period: period of time from index date to the end of drug treatment determined by having continuous record of prescription with less than 14 days of gap in prescription (grace period) or by switching to another OAC (end of index treatment is then consider to occur the day before the prescription of the new OAC)
4. Follow-up period: the day after index date to the earliest of treatment discontinuation, day before switch, end of continuous enrolment in the database, end of study period or death.

Inclusion criteria
1. >18 year-old with confirmed diagnosis of non-valvular atrial fibrillation (NVAF, ICD 10 code I48)
2. New starters of dabigatran or warfarin

3. No prescription of other OACs for12 months prior to the index date, defined as the first prescription of OACs (the period is defined as baseline period)
4. Has an index date between 14th of March 2011 to 30 June 2016

Exclusion criteria
1. Having less than 12 months of enrolment prior to the index date
2. Dialysis or kidney transplant recipients in baseline period
3. Having atrial flutter, valvular AF, mechanical valve placement, rheumatic AF, mitral valve prolapse/regurge/stenosis in baseline period
4. Having record of deep vein thrombosis or pulmonary embolism <6 months before AF diagnosis in baseline period

The symptoms, diseases, or treatments in these criteria are defined by ICD-10 code, disease name, or medical care activity name (see Table 1).

Table 1 Definition of symptoms/diseases/treatment for inclusion/exclusion criteria

| Symptoms/diseases/treatment | Definition | | |
|---|---|---|---|
| | ICD10 code | Disease name | Medical care activity name |
| Dialysis | - | - | Including “dialysis” |
| Kidney transplant | T861, Z940 | - | - |
| Atrial flutter | - | Atrial flutter | - |
| Valvular AF | - | Valvular AF | - |
| Mechanical valve placement | T820 | - | Including “mechanical valve placement” |
| Rheumatic AF | I05-I09 | - | - |
| Mitral valve prolapse | I340 | - | - |
| Mitral valve regurge | I341 | - | - |
| Mitral valve stenosis | I050, I342 | - | - |
| Deep vein thrombosis | I802 | - | - |
| Pulmonary embolism | I269 | - | - |

## 9.3 VARIABLES

### 9.3.1 Exposures

Having at least one prescription of either dabigatran or warfarin defined by ATC code or generic name.

### 9.3.2 Outcomes

9.3.2.1 Primary Outcome

- Outcome name: stroke and systemic embolism
- Time frame: drug exposure period
- Safety issue. N/A
- Definition: definition of stroke and systemic embolism provided in Koretsune et al will be used for this study[8] as following.
  - ✓ Stroke: all three following conditions must be met:
    - [1] Imaging (magnetic resonance imaging (MRI) or computed tomography (CT)) is performed after a diagnosis code of atrial fibrillation.
    - [2] Diagnosis of stroke defined as I60-I64 occurs in the same month as the imaging
    - [3] Either of the following condition is met:
      - A) Rehabilitation for cerebrovascular disease within 30 days from the date of imaging
      - B) Death within 30 days from the date of imaging
  - ✓ Systemic embolism events:
    1. Retinal vascular occlusions: three following conditions must be met:
       - [1] Ophthalmic examination is performed after the date of definitive diagnosis of atrial fibrillation or cardioembolic stroke (including the day of the diagnosis).

         The second or later ophthalmic examination during the same hospitalization is excluded.
       - [2] Diagnosis of retinal vascular occlusion in the month of the date of ophthalmic examination.
       - [3] The following A) and B) are satisfied:
         - A) Prescription of anticoagulant/antiplatelet agents on the day of ophthalmic examination or the next day
         - B) Non-prescription of anticoagulant/antiplatelet agents within 30 days from the date of ophthalmic examination.
    2. Other than retinal vascular occlusions: four following conditions must be met:
       - [1] Imaging: MRI, CT, roentgenography (using a contrast medium) or vascular echo is performed after the date of definitive diagnosis of atrial fibrillation or cardioembolic stroke (including the day of the diagnosis).
       - [2] Systemic embolism (including the name of injury/disease at the time of admission) is diagnosed and recorded as the name of the disease during hospitalization in the month of the date of imaging.
       - [3] The date of imaging or the next day: Treatment

         Either of the following conditions is satisfied:
         - A) Treatment with heparin at >5,000 units or thrombectomy on the day of imaging or the next day
         - B) Death within 30 days from the date of imaging

[4] Fees for emergency medicine administration or specific intensive care management on the day of imaging are calculated.

✓ Intracranial bleeding: all four following conditions must be met:

Condition [1] is applied to the events occurred during the hospitalization after the day of definitive diagnosis of atrial fibrillation and is not applied to those during re-hospitalization.

[1] Medical history (only atrial fibrillation)

The following injury/disease name in ICD 10 does not occur in the month prior to the month of the date of definitive diagnosis:

- Cerebrovascular disease excluding sequelae of subarachnoid hemorrhage, sequelae of intracerebral hemorrhage, sequelae of stroke not specified as hemorrhage or infarction
- Intracranial injury

[2] Imaging (MRI or CT) is performed after the month of the date of definitive diagnosis of atrial fibrillation or cardioembolic stroke (including the day of the diagnosis).

The second or later imaging during the same hospitalization is excluded.

[3] Disease name

The following disease occurs in the same month as the day of imaging:

- Cerebrovascular diseases excluding sequelae of subarachnoid hemorrhage, sequelae of intracerebral hemorrhage, sequelae of stroke not specified as hemorrhage or infarction
- Intracranial injury

[4] Rehabilitation of stroke

Either of the following conditions is satisfied:

- Rehabilitation for stroke within 30 days from the date of imaging
- Death within 30 days from the date of imaging

See below tables for definition of imaging (Table 2) and other symptoms/diseases/treatment (Table 3).

Table 2 Definition of imaging for primary outcome

| Receipt code | Definition |
|---|---|
| 170011810 | CT imaging (multi-detector computed tomography) |
| 170020110 | MRI imaging (equipment with 1.5+ tesla) |
| 170033410 | CT imaging (multi-detector computed tomography) |
| 170033510 | MRI imaging (equipment with 3+ tesla) |
| 170000810 | Roentgenography (with contrast agent) |
| 160147110, 160147210<br>160150050, 160161710 | Vascular echo |

Table 3 Definition of symptoms/diseases/treatment for primary outcome

| Symptoms/diseases/treatment | Definition | | |
|---|---|---|---|
| | ICD10 code | Receipt code | ATC code |
| Atrial fibrillation | I48 | | |
| Stroke | I61-64 | | |
| Rehabilitation | | 180027410, 180027510<br>180027610, 180027710<br>180030810, 180032410<br>180032510, 180032610<br>180033910, 180034010<br>180034110, 180034210<br>180034310, 180034410<br>180043430, 180043530<br>180043630, 180043730<br>180043830, 180044310 | |
| Cerebrovascular disease | I60-I69 | | |
| Ophthalmic examination | | 160081010, 160081130,<br>160081450, 160081550,<br>160183310, 160199310,<br>160199310, 160199410 | |
| Cardioembolic stroke | I634 | | |
| Retinal vascular occlusion | H34 | | |
| Anticoagulant/antiplatelet agents | | | B01 |
| Systemic embolism | I74 | | |
| Heparin | | | B01B |
| Thrombectomy | I74, I80-I82 | | |

Table 3 (cont'd)

| | | |
|---|---|---|
| Emergency medicine administration/ specific intensive care management | | 113002610, 113010710<br>113013810, 115003010<br>160000210, 190100070<br>190116310, 190116410<br>190137810, 190138110<br>190138210, 190138310<br>190138410, 190138510<br>190138610, 190138710<br>190138810, 190138910<br>190139010, 190139110<br>190139210, 190139310<br>190139810, 190139910<br>190171910, 190172010<br>190174410, 190174510<br>190174610, 190174710<br>190174810 |
| Sequelae of Subarachnoid hemorrhage | I690 | |
| Sequelae of intracerebral hemorrhage | I691 | |
| Sequelae of stroke not specified as hemorrhage or infarction | I694 | |
| Intracranial injury | S06 | |

9.3.2.2 Secondary Outcome

- Outcome name: Major bleeding
- Time frame: drug exposure period
- Safety issue. N/A
- Definition: major bleeding is defined as any bleeding associated with hospitalization and/or blood transfusion (defined as MDV procedure code K920 ) claims. Bleeding will include the following diagnostic names with ICD 10 codes in the parenthesis, and the list is inclusive, not exclusive;
  - ✓ Subarachnoid hemorrhage (I60)
  - ✓ Intracerebral hemorrhage (I61)
  - ✓ Digestive tract hemorrhage (K922, K290)
  - ✓ Hemorrhage, not elsewhere (R58)
  - ✓ Intraocular Hemorrhage (H113, H313, H356, H431)

- ✓ Hematuria (R31, N028, N029)
- ✓ Excessive Menstruation, Hemorrhage from Uterus (N93)
- ✓ Hemathrosis (M250)
- ✓ Hemopericardium (I312)
- ✓ Hemoptysis, bleeding from airway (R04)
- ✓ Hematemesis (K920)
- ✓ Epistaxis (R040)
- ✓ Acute post-hemorrhagic anemia (D62)

[redacted]

### 9.3.3 Covariates

Logistic regression model was used to estimate propensity scores based on all covariates listed below:

- ✓ Age
- ✓ Gender
- ✓ Speciality of prescribers of OAC
- ✓ Time from AF diagnosis to initiation of OAC
- ✓ History of stroke or transient ischemic attack yes/no
- ✓ History of myocardial infarction yes/no
- ✓ History of coronary artery disease yes/no
- ✓ History of heart failure yes/no
- ✓ History of diabetes mellitus yes/no
- ✓ History of dyslipidemia yes/no
- ✓ History of arterial hypertension yes/no
- ✓ History of peripheral artery disease yes/no

- ✓ History of peptic ulcer disease yes/no
- ✓ History of dementia yes/no
- ✓ History of malignant lymphoma yes/no
- ✓ History of leukemia yes/no
- ✓ History of solid tumor cancer yes/no
- ✓ History of kidney impairment yes/no
- ✓ History of liver disease yes/no
- ✓ History of valvular disease yes/no
- ✓ History of bleeding (gastro-intestinal, etc.) yes/no
- ✓ History of hospitalization yes/no
- ✓ $CHA_2DS_2$-VASc
- ✓ HAS-BLED Score
- ✓ Year of Initiating Treatment
  Index date falling within 12 months starting from 14th of March in 2011 and then from 1st of March of each respective year in 2012 to 2016, then to 30 June 2016.
- ✓ Concomitant medication (prescription claims within the baseline period) yes/no for the following:
  - ✧ aspirin
  - ✧ ticlodipine
  - ✧ cilostazole
  - ✧ clopidogrel
  - ✧ angiotensin receptor blockers or angiotensin converting enzyme inhibitors
  - ✧ beta-blocker
  - ✧ amiodarone
  - ✧ procainamide
  - ✧ disopyramide
  - ✧ flecainamide
  - ✧ pilcicainide
  - ✧ procainamide
  - ✧ calcium-channel blocker
  - ✧ digoxin
  - ✧ diuretics
  - ✧ statins
  - ✧ proton-pump inhibitor
  - ✧ $H_2$ receptor antagonist

The disease, condition/disease for AF risk score calculation, AF risk score, and concomitant medication are defined as Table 4,Table 5 , Table 6, Table 7, Table 8.

Table 4 Definition of clinical history

| Disease | Definition | |
|---|---|---|
| | ICD10code | prescription |
| Stroke or transient ischemic attack | I60-I64, G45 | - |
| Myocardial infarction | I21-I23 | - |
| Coronary artery disease | I251 | - |
| Heart failure | I110, I130, I132, I420, I50 | Prescribed furosemide (defined by generic name) |
| Diabetes mellitus | E100, E101, E109, E110, E111, E119, E14 | Prescribed drugs used in diabetes (defined by ATC code as A10) |
| Dyslipidemia | E78 | - |
| Arterial hypertension | I10-I15 | Prescribed 2 or more types of anti-hypertensive (defined in Table 2b) |
| Peripheral artery disease | I702-I709, I71, I739 | - |
| Peptic ulcer disease | K22, K25-K28 | - |
| Dementia | F00-F03, G30 | - |
| Malignant lymphoma | C81-C88 | - |
| Leukemia | C90-C96 | - |
| Solid tumor cancer | C00-C80, C97 | - |
| Kidney impairment | N28 | - |
| Liver disease | K70-K77 | - |
| Valvular disease | I059, I089, I358, I38, I48 | - |
| Bleeding (gastro-intestinal, etc.) | K25-K29, K922 | - |

Table 5 Definition of anti-hypertensive

| Class/type | ATC code |
|---|---|
| Calcium channel blockers (CCB) | C08A0 |
| Angiotensin receptor blockers (ARB) | C09C0 |
| Angiotensin converting enzyme inhibitors (ACE) | C09A0 |
| Diuretics | C03A1, C03A2, C03A3, C03A7, C03A9 |
| Thiazide diuretic | C03A3 (Thiazide, plane), C02D0 (Rauvolfia alkaloids) |
| Beta blocker | C07A0 |
| Alpha-adrenoreceptor antagonists | C02A2 |
| Potassium-sparing agents | C03A1 |
| Others | C02A1 (Antihypertensives), C02A3 (Antihypertensives for pulmonary arterial hypertension), C09X0 (Other agents acting on the renin-angiotensin system) |
| Combination agents | C09D1 (ARB and diuretics), C09D3 (ARB and CCB) |

Table 6 Definition of condition/disease for AF risk score calculation

| Condition/disease | Definition | |
|---|---|---|
| | ICD10code | prescription |
| Congestive heart failure or left ventricular dysfunction | I110, I130, I132, I420, I50 | Prescribed furosemide (defined by generic name) |
| Stroke (ischemic stroke, transient ischemic disease, or systemic embolism) | I63, I64, G45, I74 | |
| Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque) | I21-I23, I702-I709, I71, I739, I700 | |
| Abnormal renal function | I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 | |
| Abnormal hepatic function | B150, B160, B162, B190, K704, K72, K766, I85 | |
| Stroke (ischemic stroke or transient ischemic attack) | I63, I64, G45 | |
| Bleeding | I60, I61, I62, D62, J942, H113, H356, H431, N02, N95, R04, R31, R58, K250, K260, K270, K280, K290, S063, S064, S065, S066 | |
| Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs) | | Aspirin and clopidogrel: defined by general name<br>Non-steroidal anti-inflammatory drugs defined by ATC code (EPHMRA) as M01A |
| Alcohol intake | F10, G312, G621, G721, I426, K292, K70, K860, L278, O354, T51, Z714, Z721 | |

Table 7 AF risk score calculation

| Risk score | Disease/condition | Points if present |
|---|---|---|
| $CHADS_2$ (9) | Congestive heart failure or left ventricular dysfunction | 1 |
| | Hypertension | 1 |
| | Age ≥75 years | 1 |
| | Diabetes mellitus | 1 |
| | Stroke (ischemic stroke, transient ischemic disease, or systemic embolism) | 2 |
| $CHA_2DS_2VASc$ (10) | Congestive heart failure or left ventricular dysfunction | 1 |
| | Hypertension | 1 |
| | Age ≥65 years | 1 |
| | Age ≥75 years | 1 |
| | Diabetes mellitus | 1 |
| | Stroke (ischemic stroke, transient ischemic disease, or systemic embolism) | 2 |
| | Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque) | 1 |
| | Female | 1 |
| HAS-BLED (10) | Hypertension | 1 |
| | Abnormal renal function | 1 |
| | Abnormal hepatic function | 1 |
| | Stroke (ischemic stroke or transient ischemic attack) | 1 |
| | Bleeding | 1 |
| | Labile international normalized ratio* | 1 |
| | Elderly Age (≥65 years) | 1 |
| | Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs) | 1 |
| | Alcohol intake | 1 |

*Not included due to unavailable information

Table 8 Definition of concomitant medication

| Drug | Definition | |
|---|---|---|
| | ATC code | Generic name |
| Aspirin | - | Aspirin, aspirin dihydroxyaluminum aminoacetate magnesium carbonate |
| Ticlodipine | - | Ticlopidine hydrochloride |
| Cilostazole | - | Cilostazole |
| Clopidogrel | - | Clopidogrel sulfate |
| ARB or ACE | C09A0, C09C0, C09D1 | - |
| Beta blocker | C07A0 | - |
| Amiodarone | - | Amiodarone hydrochloride |
| Procainamide | - | Procainamide hydrochloride |
| Disopyramide | - | Disopyramide, disopyramide phosphate |
| Flecainide | - | Flecainide hydrochloride |
| Pilsicainide | - | Pilsicainide hydrochloride |
| CCB | C08A0 | - |
| Digoxin | - | Digoxin, metildigoxin |
| Diuretics | C03A1, C03A2, C03A3, C03A7, C03A9 | - |
| Statins | C10A1 | - |
| Proton pump inhibitor | A02B2 | - |
| $H_2$ receptor antagonist | A02B1 | - |

## 9.4 DATA SOURCES

MDV clinical database is health insurance claim database. As of end of February 2016, MDV has accumulated commercial claims database for both in and outpatients consisting of medical administrative claims records from more than 12.94 million patients from 230 large acute care DPC hospitals. Lab results are also available but number of hospitals providing with lab test results are limited.
Study period is from 14 Mar 2010 to 30 June 2016 in MDV database at the time of study protocol approval.
The MDV database is broadly representative of the Japanese population with similar distribution compared to the Japanese general population There is research experience using the data, 19 publications, 5 conference presentations (as of Aug 2015).

## 9.5 STUDY SIZE

This study plans no formal hypothesis testing. The planned analyses are descriptive in nature and results of statistical tests are to be interpreted in an exploratory manner. For each treatment group, the available sample size is determined by feasibility assessments of the previous study 1160.279 according to the pre-specified time window and inclusion/exclusion criteria, and not by formal sample size justifications. Therefore, the purpose of the power assessments described in this section is to illustrate the precision of the effect estimates that can be achieved given the feasible sample size.

The expected sample size of dabigatran new starters meeting inclusion/exclusion criteria after matching has been estimated to be 4,427 from the previous study 1160.279. This expected sample size is considered to have sufficient precision, defined as having less than 10% chance of the upper bound of 95% confidence interval of hazard ratio (HR) exceeding 1.378, which was an FDA recommended non-inferioity margin for effectiveness at the planning stage of RE-LY study.

Hori et al reported that the incidence of stroke and systemic embolism in the Asian subgroup of RELY study was 3.06%/year (53 events/926 patient year).[11] In the feasibility study (CTMS 1160.279), the percentage of patients receiving high dose of dabigatran or 300 mg per day was 21% and the rest or 79% was receiving equal to or less than 220mg per day. According to the Asian subgroup reported by Hori, the observed hazard ratio of warfarin to dabigatran for the endpoint of stroke and systemic embolism was 0.45 and 0.81 for 300mg and 220mg daily dose group respectively. The combined assumed hazard ratio for MDV database will therefore be Exp (log(0.45) x 0.21 + log(0.81) x 0.79 )or 0.716.

Table 9 Sample size calculation

| follow-up(y) | N per group | Event Rate (/y) | NI Margin | Power (non-inferioirty) |
|---|---|---|---|---|
| 0.40487 | 4421 | 0.025 | 1.378 | 0.987 |
| 0.40487 | 4421 | 0.025 | 1.378 | 0.944 |
| 0.40487 | 4421 | 0.025 | 1.378 | 0.846 |
| 0.40487 | 4421 | 0.025 | 1.378 | 0.692 |
| 0.40487 | 4421 | 0.025 | 1.378 | 0.507 |
| 0.40487 | 4421 | 0.03 | 1.378 | 0.996 |
| 0.40487 | 4421 | 0.03 | 1.378 | 0.974 |
| 0.40487 | 4421 | 0.03 | 1.378 | 0.905 |
| 0.40487 | 4421 | 0.03 | 1.378 | 0.770 |
| 0.40487 | 4421 | 0.03 | 1.378 | 0.583 |
| 0.40487 | 4421 | 0.035 | 1.378 | 0.999 |
| 0.40487 | 4421 | 0.035 | 1.378 | 0.988 |
| 0.40487 | 4421 | 0.035 | 1.378 | 0.943 |
| 0.40487 | 4421 | 0.035 | 1.378 | 0.832 |
| 0.40487 | 4421 | 0.035 | 1.378 | 0.650 |

Assuming stroke/SE event rate of 0.03/PY and HR of 0.716, the probability of the upper bound of 95% CI exceeding 1.378 is considered to be less than 10%. Lower event rate or narrower margin will reduce power.

## 9.6 DATA MANAGEMENT

Data are provided as electrical data formatted csv by MDV and stored and managed in Milliman Inc.
SAS and Microsoft Excel are used for statistics.

## 9.7 DATA ANALYSIS

### 9.7.1 Main analysis

Propensity Score Matching
To reduce channelling bias, dabigatran and warfarin study groups will be established using PS matching method, on a 1:1 fixed ratio. The nearest neighbour method of propensity score matching within a caliper of 0.10 of the standard deviation of the estimated logit will be used to select the matched samples. All pre-defined variables has been evaluated in CTMS 1160.279 for inclusion into the model. Covariates with less than 10 patients present in the data was eliminated as well as CHADs which showed high co-linearity with CHADsVASc which was eliminated from the model. Otherwise, all pre-defined variables will be used. For further detail of the methodology of PS matching, please see the study protocol CTMS 1160.279.

For the primary outcome
Incidence rates of each treatment cohort (warfarin and dabigatran) will be provided, and all analysis will be conducted on the PS matched sample. The hazard ratio (HR) of stroke/systemic embolism for the dabigatran cohort as compared to the warfarin cohort and its 95% confidence interval (CI) will be estimated from the PS matched cohort using a Cox regression model with treatment group as the dependent variable. No additional covariates are considered in the Cox model as no residual imbalance was identified after PS matching (1160.276 study report, c15432368)" There will be no formal hypothesis testing. Kaplan Meier analysis with the number of patients at risk during the follow-up period after the index date and the number of events for ischemic stroke and major bleeding will be provided.

For the secondary outcome
Same analysis method will be utilized to calculate HR for the outcome of major bleeding.

[redacted]

## 9.8 QUALITY CONTROL

Milliman will conduct a quality check as below:
Calculation check: both of program codes for calculation and the data codes used the calculation will be checked by different person from that who calculated.

Pre-release peer review: comprehensive check on methodology, calculation process, and consistency of results will be performed by a qualified peer-reviewer.
Post-release peer review: comprehensive check on the project will be conducted by qualified peer-reviewer belonging to another office.

## 9.9 LIMITATIONS OF THE RESEARCH METHODS

•
- Unobservable factors or factors not captured in the database such as laboratory data not equally distributed in the treatment groups that may also influence the outcomes could lead to unobserved confounding.
- The anticipated sample size might be limited which might lead to imprecise results. Therefore the study can only be considered to be exploratory. Based on the expected small sample size there is also the risk of pure chance findings. No hypothesis testing is planned,
- All information of each patient is from consent giving DPC hospitals. If patients have visits to other non-DPC medical institutions, these data are not included in the MDV data.

## 9.10 OTHER ASPECTS

None

## 9.11 SUBJECTS

The source population is Japanese patients who have claims data in MDV commercial database. In order to have claims in the database, the patients must have received some medical intervention, out or in-patient hospital visit, or pharmacy prescription from the DPC hospitals in Japan. DPC hospitals are large hospitals, often associated with medical schools or government funding, providing both acute and chronic medical care in Japan. Compared to non-DPC hospitals, they tend to provide more specialized, intensive medical care in addition to outpatient primary care tending to chronic disease requiring non-urgent care. MDV database has contractual agreement to receive claims data from approximately 12% of all DPC hospitals in Japan, and the selection is based on the willingness on the side of DPC hospitals to receive either financial compensation or data services from MDV. The inclusion and exclusion criteria are intended to select those Japanese atrial fibrillation patients who have non-valvular etiology and have newly initiated oral anti-coagulants for stroke prevention. The data cut-off of 14 Mar 2011 to 30 June 2016 is to select those claims that have occurred after the launch of dabigatran and to the most recent available data cut from MDV at the time of protocol writing.

### 9.11.1 Cases

Not Applicable

### 9.11.2 Controls

Not Applicable

### 9.12 BIAS

Unobservable factors or factors not captured in the database such as laboratory data not equally distributed in the treatment groups that may also influence the outcomes could lead to unobserved confounding.. In order to minimize bias, this study will include only new users (treatment-naïve initiators) of warfarin and dabigatran and use propensity score matching.

## 10. PROTECTION OF HUMAN SUBJECTS

As this is a study based on databases using anonymous and personally unidentifiable data; therefore protection of human subjects is not applicable for this study.

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

The outcomes of the study are the baseline characteristics (pre-treatment) and medication prescriptions.. This is a non-interventional study based on existing data, in which all patient data will be de-identified and analyzed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable for this study.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A manuscript describing this work will be submitted for publication in a peer-reviewed journal.
Target of final study report (publication submission): Sep 2017

# 13. REFERENCES

## 13.1 PUBLISHED REFERENCES

Reference:
1. Connoly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009; 361: 1139-51
2. Graham DJ, et al. Stroke, bleeding and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. JAMA Intern Med 2016; 176: 1662-1671
3. Larsen TB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation; propensity weighted nationwide cohort study. BMJ 2016;353: i3189
4. Gorst-Rasmussen A, et al. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation; comparative effectiveness and safety in Danish routine care. Pharmacoepidemiology and Drug Safety 2016; 25: 1236-1244
5. ChanYH, et al. Thromboembolic, Bleeding, and mrtality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation. J Am Coll Cardiol 2016; 68: 1389-1401
6. Yamaguchi T, et al. The epidemiological study of venous thromboembolism and bleeding events using a Japanese healthcare database –validation study-. Jpn J Drug Inform 2015; 17: 87-93
7. Yamana H, et al. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol 2017; pii: S0917-5040(17)30003-5.
8. Koretsune Y, et al. Usefulness of a healthcare database for epidemiological research in atrial fibrillation, J Cardiol 2016; pii: S0914-5087(16)30289-1.
9. Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001; 285(22): 2864-70.
10. Larsen TB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016; 353: i3189.
11. Hori M, et al. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation-sub-analysis in Japanese population in RE-LY trial. Circ J 2011; 75: 800-805

## 13.2 UNPUBLISHED REFERENCES

# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| | None | | |
| | | | |
| | | | |

# ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

None

# ANNEX 3. ADDITIONAL INFORMATION

None

**APPROVAL / SIGNATURE PAGE**

**Document Number: c17002710** **Technical Version Number:1.0**

**Document Name:** non-interventional-study-protocol-1160-0288

**Title:** Comparative Effectiveness and Safety between Warfarin and Dabigatran Using Real World Claims Data of Japanese Non-valvular Atrial Fibrillation Patients

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Approval-[redacted] Medical Affairs | [redacted] | 11 Jul 2017 10:54 CEST |
| Approval-[redacted] Medicine | [redacted] | 11 Jul 2017 12:24 CEST |
| Author-Trial Clinical Monitor | [redacted] | 13 Jul 2017 03:49 CEST |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|