Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

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BI Investigational Product(s):	Prazaxa (Dabigatran etexilate)
Title:	Treatment patterns of newly initiated oral anticoagulants on Japanese non-valvular atrial fibrillation patients using a Japanese claims database
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Active substance:	Dabigatran, warfarin, apixaban, rivaroxaban, edoxaban
Medicinal product:	Dabigatran, warfarin, apixaban, rivaroxaban, edoxaban
Product reference:	Not applicable
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Joint PASS:	No
Research question and objectives:	1. To understand the treatment patterns of OACs and baseline patient characteristics of Japanese NVAF patients 2. To determine whether warfarin and dabigatran new user group can be balanced using propensity score matching using pre-specified baseline covariates 3. As an exploratory analysis, to assess mean duration of on-therapy follow-up time in database
Country(-ies) of study:	Japan
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EU-QPPV:	Not Applicable
Signature of EU-QPPV:	Not Applicable
Date:	11 Nov 2016

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2. LIST OF ABBREVIATIONS

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
COPD	Chronic Obstructive Lung Disease
DM	Diabetes Mellitus
DPC	Diagnosis Procedure Combination
ICD	International Classification of Diseases
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants
PVD	Peripheral Vascular Disease
SD	Standard Deviation
SE	Standard Error

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa			
Name of active ingredient:		Dabigatran etexilate	
Protocol date: 11 Nov 2016	**Study number:** 1160.279	**Version/Revision:** Version 1	**Version/Revision date:**
Title of study:	Treatment patterns of newly initiated oral anticoagulants on Japanese non-valvular atrial fibrillation patients using a Japanese claims database		
Rationale and background:	Real-world data about the characteristics of patients with NVAF initiating an OAC in Japan has been scarce to date. The purpose of this study is to describe the characteristics of such patients in the MDV database.		
Research question and objectives:	1. To understand the treatment patterns of OACs and baseline patient characteristics of Japanese NVAF patients 2. To determine whether warfarin and dabigatran new user group can be balanced using propensity score matching using pre-specified baseline covariates 3. As an exploratory analysis, to assess mean duration of on-therapy follow-up time in database		
Study design:	A retrospective, observational study using health insurance claims data		
Population:	Medical Data Vision (MDV) clinical database is used. Inclusion criteria: patients aged >18 year-old with confirmed diagnosis of NVAF (ICD 10 code I48), being new starters of either dabigatran, warfarin, apixaban or edoxaban, having 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)), and having an index date between 14 Mar 2011 to 30 June 2016 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		
Data sources:	MDV clinical database. The database is health insurance claims database. As of end of February 2016, MDV provides commercial claims database for in and out-patients consisting of medical records		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa			
Name of active ingredient:		Dabigatran etexilate	
Protocol date: 11 Nov 2016	**Study number:** 1160.279	**Version/Revision:** Version 1	**Version/Revision date:**
	from more than 12.94 million patients from 230 large acute care DPC hospitals. . Observation period is planned from 14 Mar 2010 to 30 June 2016 considering the launch date of dabigatran.		
Study size:	This is a feasibility study to assess whether sufficient study eligible patients and baseline characteristics are obtainable from the MDV database. The sample size for a patients' group with prescribed each OAC will be estimated by multiplying the number of patients meeting the eligibility criteria by the estimated on-treatment follow-up duration independent of treatment.		
Data analysis:	No formal hypothesis testing using statistical analysis will be conducted in this study. Descriptive statistics of each OAC will be conducted for the baseline characteristics and treatment status on index date. Propensity score matching will be conducted to see if sufficient sample sized propensity score matched group can be identified in the database.		
Milestones:	Start of Data Analysis: 10 Nov 2016 End of Data Analysis: 30 Nov 2016 Study Report: 15 Dec 2016		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
	None			

6. MILESTONES

Milestone	Planned Date
Start of data analysis	10 Nov 2016
End of data analysis	30 Nov 2016
Final report of study results:	15 Dec 2016

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 ICD10 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.
MDV provides commercial claims database for inpatient and outpatient consisting medical records from more than 12.94 million patients from 230 large acute/primary care DPC hospitals as of Feb 2016. According to the data released by the company in Sept 2016 [1], in one year period between July 2015 and June 2016, cumulative number of patients in the claims database was 7,546,862 patients. 82% of patients (6,152,732) were associated with outpatient claims only, while 15% of patients (1,131,869) had claims from both in and out-patient care. Only 3% of patients (262,261) had exclusively in-patient claims. MDV data collects data from DPC hospitals which provides both outpatient and inpatient service with associated claims collected from either source. There can be only outpatient claims from a patient since patients do not need to be hospitalized to be treated at these DPC hospitals, thus leading to a much higher proportion of patients with exclusively out-patient claims as stated above. Patients with more severe disease may tend to go to DPC hospital outpatient clinics instead of going to small private clinics, which may lead to loss of generalizability of findings from this study to the Japanese general population. Laboratory data is available for approximately 10% of patients contained in the database, and therefore will not be explored in this current study. Currently, SHORT-J study is analyzing the difference in length of hospital stay between warfarin and dabigatran using in-patient data from this MDV database.

Real-world data about the characteristics of patients with NVAF initiating an Oral Anti-coagulant therapy (OAC) in Japan has been scarce to date. The purpose of this study is to describe the characteristics of such patients in the MDV database. This study could also be useful to gain further insights to the prescribers' adherence to the recently revised anti-coagulation treatment guideline [2] and on the comparability of patients on vitamin K antagonist and dabigatran in the MDV setting to inform potential additional studies looking into treatment outcome.

8. RESEARCH QUESTION AND OBJECTIVES

1. To understand the treatment patterns of OACs and baseline patient characteristics of Japanese NVAF patients
2. To determine whether warfarin and dabigatran new user group can be balanced using propensity score matching using pre-specified baseline covariates.
3. As an exploratory analysis, to assess mean duration of on-therapy follow-up time in database

9. RESEARCH METHODS

9.1 STUDY DESIGN

Study design
- A retrospective, observational, feasibility study using health insurance claims data

Treatments Considered:
- Dabigatran, warfarin, apixaban, rivaroxaban, and edoxaban

Strength of the study design
- Up-to-date information can be obtained and nationwide actual treatment status can be illustrated with using large-scale real-world database.

Outcomes to Assess Feasibility
- Primary endpoints: type and dosage of OAC drug prescribed for Japanese NVAF patients.
- Secondary endpoints: patient baseline characteristics of Japanese NVAF patients in each group.
- Main measures: numbers of patients newly prescribed with dabigatran, warfarin, apixaban, and edoxaban, baseline characteristics (age, sex, history of diseases, medications), dosage of OAC, year of initiating treatment, previous and concomitant medication, complications, observation period.

Potential limitation
- Generalizability of findings from this study may be limited outside of the population.
- The data held in MDV database is collected from DPC hospitals, not general practitioner data. Data from DPC hospitals may contain out-patient data with greater disease severity than those exclusively seen by small medical clinics.
- Information of each patient is from consent giving DPC hospitals. If patients have visits other medical institutions, these data are not included in the MDV data.
- Variables available in the database may miss important drivers of treatment decision.
- Sufficient baseline covariates may not be available in the database to conduct propensity score matching.

9.2 SETTING

MDV clinical database is used.

Inclusion criteria
1. >18 year-old with confirmed diagnosis of NVAF (ICD 10 code I48)
2. New starters of dabigatran, warfarin, apixaban, and edoxaban
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

9.3 VARIABLES

9.3.1 Exposures

Having a prescription claim of dabigatran, warfarin, apixaban, or edoxaban from 14 Mar 2011.

9.3.2 Outcomes to Assess Feasibility

9.3.2.1 Primary outcomes

Type and dose of OAC drug prescribed for new users of anticoagulants with NVAF Secondary outcomes

9.3.2.2 Secondary outcomes

Baseline characteristics of new users of anti-coagulants with NVAF

9.3.2.3 Further outcome

OACs pooled “Treatment Independent” average follow-up period: number of days beginning on the index date to the end on the date of discontinuation of the index exposure, date of switch to an anticoagulant different from the index exposure, end of continuous eligibility of a patient in the health plan (disenrollment), end of observation period, or date of death of the patient; whichever occurs earlier. The drug exposure period will be defined as the duration from index date to the end of follow-up.

9.3.3 Covariates

Logistic regression model will be 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
- ✓ $CHADS_2$
- ✓ 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

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.

9.5 STUDY SIZE

This is a feasibility study to assess whether sufficient study eligible patients and baseline characteristics are obtainable from the MDV database.
The sample size for a patients' group prescribed each OAC will be estimated by multiplying the number of patients meeting the eligibility criteria by the estimated on-treatment follow-up duration independent of treatment.

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

- Descriptive statistics of each OAC will be conducted for the baseline characteristics and treatment status on index date:
  - ✓ Number of patients
  - ✓ Age (mean ± SE, mean ± SD)
  - ✓ Sex
  - ✓ Clinical history and co-morbidity (peptic ulcer disease, dementia, COPD, PVD, DM, leukemia, solid tumor, malignant lymphoma, liver disease, CHF)
  - ✓ Previous and concomitant medications
  - ✓ Year and month of index date
  - ✓ Time from AF diagnosis to first NOAC prescription
  - ✓ Type and dose of OAC
  - ✓ Length of observation period after index date

9.7.2 Exploratory analysis

To assess for potential selection bias, the dabigatran and warfarin study cohorts will be matched on their baseline characteristics using the propensity score matching (PSM) method, on a 1:1 fixed ratio basis. The Nearest Neighbor 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. The propensity score will be defined as the probability of being treated with dabigatran based on a set of baseline characteristics. It will be derived from predicted probabilities of treatment initiation estimated in a logistic regression model which considers the covariates listed in section 9.3.3

Please refer to section 9.3.3 for the list of covariates

The number of covariates considered can be adapted to the number of patients available (at least 10-20 patients on dabigatran per coefficient of the model). Mutually correlated, and/or frequently missing covariates will be disregarded. Frequencies of missing covariates will be tabulated. A simple linear correlation between continuous covariates including rank covariates will be graphically and descriptively investigated using scatter plots and

correlation matrix of Kendall's and Spearman's rank correlations. For categorical covariates, a two-way cross table of a covariate pair whose chi square p-value is less than 0.2 will be presented. . For each covariate, estimates, standard error, and Wald test p-value will be tabulated. PSMs using different sets of covariates will be compared descriptively and graphically using AIC, C-statistic and ROC curve.

To examine the balancing property of characteristics, standardized difference will be calculated for variables included in the propensity score model for both the unmatched population as well as for the matched sample. The matched cohorts are considered balanced if the absolute value of the standardized difference was less than 10%.
The distribution of baseline characteristics and of the propensity score will be presented before and after the matching process.

As a sensitivity analysis, the following alternative approaches will be considered:
- PSM based on matching ratios of 1 : k (where k depends on data)
- PSM using calipers of 0.15 and 0.20 x standard deviation
- PSM using covariates selected by stepwise method

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-review.
Post-release peer review: comprehensive check on the project will be conducted by qualified peer-review belonging to another office.

9.9 LIMITATIONS OF THE RESEARCH METHODS

- Generalizability of these findings may be limited outside of this population. 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.
- Variables available in the database may miss important drivers of treatment decision.
- Sufficient baseline co-variates may not be available in the database to conduct propensity score matching.

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. Since clinical outcome will not be examined, case ascertainment or validation data will not be provided.

9.11.1 Cases

Not Applicable

9.11.2 Controls

Not Applicable

9.12 BIAS

- Generalizability of the data to be obtained may be limited outside of this population
- All information of each patient is from consent giving DPC hospitals. If patients have visits to other medical institutions, these data are not included in the MDV data.
- MDV database is composed of data from patients who were either seen in ambulatory care clinic or hospitalized in DPC hospitals so that more severe patient may be included in the database.

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. We will not be looking at outcomes during the treatment period; therefore 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.

13. REFERENCES

13.1 PUBLISHED REFERENCES

[1] Percentage of inpatient and outpatient. MDV Mail Magazine. 2016 Sept;8:1.
[2] JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ J. 2014;78(8):1997-2021.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
	None		