NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Revision	Effective Date	Summary of Revisions
1.1	*2018/5/08*	*Schedule(Milestone) has been revised*

[redacted]

Study information

Title	Safety and effectiveness evaluation of patients with non-valvular atrial fibrillation treated with OACs: Comparison between NOACs and warfarin (CER3)
Protocol number	B0661120
Protocol version identifier	1.1
Date of last version of protocol	08MAY2018
EU Post Authorisation Study (PAS) register number	Not applicable (this study is not PASS)
Active substance	B : Blood and blood forming organs B01: Antithrombotic agents B01A : Antithrombotic agents B01AF: Direct factor Xa inhibitors B01AF02: Apixaban
Medicinal product	Eliquis (Apixaban)
Research question and objectives	The research questions are: 1) is there any difference in the risk of major bleeding and composite of ischemic stroke, hemorrhagic stroke or systemic embolism (stroke/SE) between patients treated with warfarin and those treated with one of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban) in OAC naïve NVAF patients who start treatment with OACs. The primary objective is to compare the risk of major bleeding and stroke/SE in warfarin-apixaban matched cohorts, warfarin-dabigatran matched cohorts, warfarin-edoxaban matched cohorts and warfarin-rivaroxaban matched cohorts.
Author	PPD , PPD PPD

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial fibrillation
DPC	Diagnosis Procedure Combination
ICD	International Statistical Classification of Diseases and Related Health Problems
INR	International Normalized Ratio
IPTW	Inverse Probability Treatment Weighting
MDV	Medical Data Vision
MI	Myocardial Infarction
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non valvular atrial fibrillation
OAC	Oral anticoagulant
PSM	Propensity Score Matching
RCT	Randomized control trial
RWD	Real World Data
SAP	Statistical Analysis Plan
SE	Systemic embolism
TIA	Transient ischemic attack

1. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD	PPD	PPD	PPD

2. ABSTRACT

Title: Safety and effectiveness evaluation of patients with non-valvular atrial fibrillation treated with OACs: Comparison between NOACs and warfarin (CER3)
Version 1.0, Mar.14, 2018. PIH IM CV/MET Medical Affairs, PPD

Rationale and background: Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. It has been reported that AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. An anticoagulation therapy is a critical treatment to prevent thromboembolism in non-valvular AF (NVAF) patients. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment for prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs),

dabigatran, was introduced with approval for stroke prevention in NVAF patients in March 2011, followed by rivaroxaban in January 2012, apixaban in December 2012, and edoxaban in September 2014 in Japan. NOACs provide more convenient therapeutic options and have been demonstrated at least equivalent efficacy compared to warfarin in Phase 3 clinical trials[4-7]. Apixaban is one of the four NOACs marketed in Japan and has been demonstrated superiority versus warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in patients with atrial fibrillation in Phase 3 clinical trial[6]. However, its safety and effectiveness remains unknown in real-world clinical practice in Japan. Previously we have shown in the CER1 study[8] that bleeding risks are also less in real world clinical practice in Japan compared to warfarin but effectiveness, that is, prevention of stroke, has not been evaluated yet. This study will evaluate the risk of stroke/SE as well as the risk of bleeding in the real world settings in Japan in patients with NVAF who initiated any of OACs (apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin).

Research question and objectives: The research questions are: 1) is there any difference in the risk of major bleeding and of a composite of (ischemic and hemorrhagic) stroke/SE between patients treated with warfarin and those treated with one of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban) in OAC naïve NVAF patients who start treatment with OACs.

The primary objective is to compare the risk of major bleeding and composite of (ischemic and hemorrhagic) stroke/SE in warfarin-apixaban cohorts, warfarin-dabigatran cohorts, warfarin-edoxaban cohorts and warfarin-rivaroxaban cohorts.

Study design: This is a retrospective, non-interventional observational study using the database provided by Medical Data Vision Co. Ltd. (MDV Co. Ltd.) (data set from March 1st, 2011 to December 31st, 2017) designed to evaluate the difference in safety (major and any bleeding) and effectiveness (composite of stroke/SE) in the matched cohorts created by using a propensity score matching method or a stabilized IPTW (inverse probability of treatment weighted) method. Comparisons of apixaban *versus* warfarin, dabigatran versus warfarin, edoxaban versus warfarin and rivaroxaban versus warfarin will be performed.

Population: Data from OAC treatment-naïve Japanese patients with NVAF initiating OAC treatment will be used for the analysis. Further information on patient selection, enrollment and follow-up time periods are included in Subsections 7.2 below.

Variables: Index treatment of OACs; outcome measures including major bleeding, any bleeding, stroke/SE and demographic and clinical characteristics of the patients.

Data sources: Medical Data Vision database

Study size: The required number of eligible patients for each cohort is estimated in Subsection 7.5 below and also in the Statistical Analysis Plan (SAP).

Data analysis: Detailed methodology for data analysis will be described in the SAP. Baseline patient demographic information will be compared among the warfarin and each NOAC cohorts by appropriate tests (e.g., t-test, Mann Whitney-U test, chi-square test) based on the distribution of the measures. Both propensity score matching (PSM) and stabilized IPTW methods will be used to estimate treatment effects of NOACs compared with warfarin. To estimate hazard ratio and 95% confidence intervals of each NOAC compared with warfarin using univariable Cox proportional hazards models (OAC treatment as a single variable) will be used.

Milestones: Data extraction from MDV database: Mar.19 - Mar.26, 2018; Analysis: Apr.01 - Apr.16, 2018; Manuscript submission: JUL. 30th, 2018.

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason

4. MILESTONES

Milestone	Planned date
Start of data collection	15 MAY 2018
End of data collection	21 MAY 2018
Final study report	1 OCT 2018

5. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. AF can be categorized into three main categories based on patient characteristics: lone atrial fibrillation – AF in the absence of overt cardiovascular disease or precipitating illness[9]; non-valvular AF (NVAF) – presence of AF without concurrent rheumatic mitral valve disease or history of mitral valve repair or prosthetic heart valve; and secondary AF-AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease. Anticoagulation therapy is important to prevent thromboembolism in patients with NVAF. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment and prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, was introduced with approval for NVAF treatment in March 2011, followed by rivaroxaban in January 2012, apixaban in December 2012, and edoxaban in September 2014 in Japan.

Although randomized control trials (RCTs) aimed at head-to-head comparison with placebo or a reference drug may provide evidence of safety and efficacy of treatments at the highest level, there are potential limitations derived from a limited number of pre-selected patients and strict patient eligibility criteria with regard to age, comorbidities, and concomitant medications. Accordingly, these studies may not accurately represent what happens when drugs are used in general clinical practice. Recently, in order to overcome the drawbacks of RCTs and corroborate the evidence from RCTs, real-world evaluations of drugs have been conducted. As for anticoagulants, there are some studies that have evaluated safety and effectiveness of NOACs such as apixaban, dabigatran, and rivaroxaban in the real-world setting and the results were similar to those obtained from RCTs[4-7]. However, these studies are not sufficient, especially for effectiveness evaluation, and real-world data (RWD) specific to each country or region are also required. For example, Asian populations, including Japanese population, are known to be more prone to intracranial hemorrhage when treated with warfarin[10]. Japan is a rapidly aging society with a large proportion of the population aged 75 years or older. Unfortunately, there have been few large-scale, real-world studies to investigate safety and effectiveness of NOACs in patients with NVAF receiving NOACs versus warfarin in Japan.
The objective of this study is to compare the risk of incidence of stroke and bleeding among patients with NVAF newly prescribed any of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban), versus newly prescribed warfarin using a nation-wide administrative claims database.

This retrospective study is conducted voluntarily by Pfizer. This study will not be conducted as post-authorization safety study (PASS) [redacted] according to the decision by the business process owner [redacted].

6. RESEARCH QUESTION AND OBJECTIVES

The research questions:

1. Are there any differences in the risk of major bleeding and any bleeding between NOACs and warfarin in the general practice settings in Japan?
2. Are there any differences in the risk of stroke/systemic embolism between NOACs and warfarin in the general practice settings in Japan?

The primary objective of the study compare both the risk of stroke/ SE and of bleeding events among patients with NVAF initiating treatment with one of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban) versus warfarin.

The secondary objectives are

1. to compare the risk of major GI bleeding, any GI bleeding, and intracranial Hemorrhage between warfarin-initiators and NOAC-initiators
2. to compare the risk of ischemic stroke, hemorrhagic stroke or SE between warfarin-initiators and NOAC-initiators

CCI [redacted]

7. RESEARCH METHODS

7.1. Study design

This is a retrospective observational study using data from the MDV database (data set from March 1st, 2011 to December 31st, 2017). Among patients registered in the database patients are selected based on the inclusion and exclusion criteria (see blow). The first observed prescription of apixaban, dabigatran, edoxaban, rivaroxaban or warfarin is used to identify the patient's index date (date of the first prescription of any OACs is defined as "index date") and treatment cohort. Study measures include: (1) for safety evaluation: major bleeding and any bleeding; (2) for effectiveness evaluation: a composite of ischemic stroke, hemorrhagic stroke or SE.
The follow-up period is variable, and will begin on the next day of the index date and continue until the earliest of the following scenarios – occurrence of target outcome event (details available in Section 8.2); discontinuation of the index OAC; switching from the index OAC; withdrawal from the database.

7.2. Setting

This study uses data from the MDV database, which includes the data used for both inpatient and outpatient insurance claims by hospitals according to the Diagnosis Procedure Combination (DPC) procedure.

The study population will consist of adults with NVAF who are newly prescribed apixaban, dabigatran, edoxaban, rivaroxaban or warfarin. Follow-up time period starts from the next day of the index date, and ends depending on following outcomes which observed first.

1. Major bleeding when the target outcome for the analysis is major bleeding.
2. Composite of (ischemic or hemorrhagic) stroke and SE when the target outcome for the analysis is the composite endpoint.
3. Any bleeding when the target outcome for the analysis is any bleeding.
4. Discontinuation of the index OAC: The index treatment will be considered to be "discontinued" if the index OAC is not prescribed within 45 days after prescription refill date (calculated from the last refill date plus days of supply) of the index OAC, even though the patient has >1 medical encounter records after more than 45 days following the prescription refill date. The supposed prescription refill date is regarded as the last day of the follow-up for discontinued patients.
5. Switching from the index OAC: The index treatment is regarded as "switched" if non-index OAC is prescribed within 45 days after prescription refill date of the index OAC when the patient has 1> medical encounter records after more than 45 days following the prescription refill date. The switched day is regarded as the last day of the follow-up for the switched patients.

6. Withdrawal from the database: The patients are regarded as “withdrawal” from the database if the index OAC is not prescribed within 45 days after prescription refill date of the index OAC and there is no data of the patient on the database after prescription refill date. The last medical encounter is regard as the last day of the follow-up for patients withdrawn from the database.

7.2.1. Inclusion criteria

Patients must meet all of the following criteria to be eligible for the study:

1. Diagnosed with AF anytime in the baseline period or on the index date, also have definitive diagnosis of AF anytime in the baseline period, on the index date, or post-index period.
2. Prescribed one of the index OACs (apixaban, dabigatran, edoxaban, rivaroxaban or warfarin) on or after the day of AF diagnosis. The first observed prescription will be used to identify the patient’s index date and treatment cohort
3. No use of the any OACs during the baseline period (the 180 days before the index date)
4. Age of 18 years or older on the index date.

7.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Having a diagnosis of valvular atrial fibrillation, post-operative atrial fibrillation, rheumatic atrial fibrillation or mechanical-valvular atrial fibrillation during the baseline and post-index period
2. Having a cardiac surgery procedure record during the baseline period
3. Having a joint replacement procedure record during the baseline period
4. Having a procedure of prosthetic heart valve during the baseline period
5. Having a diagnosis of venous thromboembolism during the baseline period
6. Female patients with pregnancy during the follow-up period
7. Patients prescribed “off-label” doses of OACs (per Japanese package insert of each OAC) or patients treated with OAC but in “off-label” or “contraindicated” manners.

7.3. Variables

Demographic and clinical characteristics are collected during the baseline period or at the index date.

Table 1: Demographic and clinical information of patients

Variable	Obtained from	Operational definition
Sex Category	Index date	Dichotomous variable equals 1 if sex is male and 2 if female
Age	Index date	Age (in years) at the index date
Physician specialty	Index date	Dichotomous variable equals 1 if a physician specialty on the index date is categorized into a cardiac specialty and 0 if others. Following specialties will be categorized as the cardiac specialty: cardiology stroke, cardiovascular surgery, pediatric cardiology, neurosurgery, cardiovascular medicine, and neurology. If there are ≥1 specialties but including the cardiac specialty, the physician specialty will be regarded as the cardiac specialty.
Hospital size (<500 beds or not)	Index date	Dichotomous variable equals 1 if hospital size on the index date is <500 beds and 0 if ≥500 beds.
Hospitalization status on index date	Index date	Dichotomous variable equals 1 if hospitalization status is inpatient and 0 if outpatient.
$CHADS_2$	Baseline period	$CHADS_2$ score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, and stroke or TIA.
CHA_2DS_2-VASc	Baseline period	Score calculated by appointing 1 point each for congestive heart failure/left ventricle dysfunction, hypertension, diabetes, vascular disease (prior MI, peripheral arterial disease, or aortic plaque), age between 65-74, female gender; and 2 points each for age >75 years and prior stroke, TIA, or thromboembolism.
PT-INR (Prothrombin time-international normalized ratio)	Baseline period	Continuous variable. * Only available for patients treated with warfarin
Heart failure diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for heart failure ICD-10 or disease codes during the baseline period.
Coronary heart disease diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for coronary heart disease ICD-10 or disease codes during the baseline period.
Peripheral arterial disorder diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for peripheral arterial disorder ICD-10 or disease codes during the baseline period.
Myocardial infarction diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for myocardial infarction ICD-10 or disease codes during the baseline period.
Hyperthyroidism or thyrotoxicosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for hyperthyroidism ICD-10 or disease codes during the baseline period.
Stroke, TIA or SE diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for Stroke, TIA or systemic embolism ICD-10 or disease codes during the baseline period.
Renal dysfunction diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for renal dysfunction ICD-10 or disease codes during the baseline period.
Liver dysfunction diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for liver dysfunction ICD-10 or disease codes during the baseline period.
Bleeding diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for bleeding ICD-10 or disease codes during the baseline period.
Hypertension diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for hyper tension ICD-10 or disease codes during the baseline period.
Diabetes mellitus diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.

Cancer diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.
Treated with antiplatelet drug in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of antiplatelet drug ATC or receipt codes during the baseline period.
Treated with NSAIDs in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of NSAIDs ATC or receipt codes during the baseline period.
Treated with gastric secretion inhibitor in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of gastric secretion inhibitor drug ATC or receipt codes during the baseline period.
Treated with statin-based drug in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of statin-based drug ATC or receipt codes during the baseline period.
Treated with anti-hypertensives in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-hypertensive ATC or receipt codes during the baseline period.
Treated with anti-arrhythmics in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-arrythmics ATC or receipt codes during the baseline period.
Treated with beta-blockers in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of beta-blockers ATC or receipt codes during the baseline period.
Treated with heparins in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 prescriptions of heparins ATC or receipt codes during the baseline period.
Cardioversion in baseline	Baseline period	Dichotomous variable equals 1 if there is ≥1 operation of cardioversion receipt codes during the baseline period.
Major bleeding in follow-up	Follow-up period	Dichotomous variable equals 1 if there are ≥1 diagnoses for major bleeding ICD-10 or disease codes during the follow-up period.
Any bleeding in follow-up	Follow-up period	Dichotomous variable equals 1 if there are ≥1 diagnoses for any bleeding ICD-10 or disease codes during the follow-up period.
Stroke/SE in follow-up	Follow-up period	Dichotomous variable equals 1 if there are ≥1 diagnoses for stroke or SE ICD-10 or disease codes during the follow-up period.

7.4. Data sources

The analysis will be based on administrative data from MDV Co. Ltd., a longitudinal database based on health insurance claims and medical records obtained from the hospitals in which the DPC payment system for utilization of both inpatient and outpatient hospital claims (percentage of inpatients is about 45%). The database provides claims data from 314 hospitals (as of June 2017) using the DPC system for medical service claims (21% of general hospitals but 55% of general beds in Japan is under the DPC system) including approximately 14 million patient data.

7.5. Study size

All eligible patients are extracted from the database and used for the analysis. In the previous study (CER2; conducted based on the data from March 1st, 2011 to December 31st, 2017 for apixaban, edoxaban and warfarin), 14,830 patients on warfarin, 16,176 patients on apixaban and 4,438 patients on edoxaban were eligible for the analysis. The required number of patients for the planned analysis and the estimated number of eligible patients for each cohort is shown in a Statistical Analysis Plan

(SAP).

7.6. Data management

Data will be securely provided by MDV Co. Ltd. All analyses will be conducted using SAS software (Version 9.0 or higher, SAS Institute, Cary, NC, USA) with study results presented in Microsoft Excel tables.

7.7. Data analysis

Baseline patient demographic information will be compared among the warfarin and NOACs cohorts by appropriate tests (e.g., t-test, Mann Whitney-U test, chi-square test) based on the distribution of the measures. A PSM method will be used to balance patient characteristics between compared cohorts (apixaban versus warfarin, dabigatran versus warfarin, edoxaban versus warfarin or rivaroxaban versus warfarin). In addition to the simple PSM (that is, without “weighting”), a stabilized inverse probability treatment weighting (IPTW) method will be also used to balance patient characteristics between groups[11] (see also *Statistical Analysis Plan*). Cox proportional hazards models (OAC treatment as a single variable) will be used to calculate the hazard ratios with 95% confident intervals. Anticoagulant type (apixaban or warfarin, dabigatran or warfarin, edoxaban or warfarin or rivaroxaban or warfarin) was included and no other covariates were included in the COX model because two cohorts were balanced after propensity score matching.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.8. Quality control

This study is a retrospective analytical study using quality controlled data in a pre-existing database, and primary data collection will not be conducted. As for the data provided, quality of the data is guaranteed by MDV Co. Ltd., which has professional teams specialized in the maintenance and improvement of data quality. All of these processes are consistently managed in-house. All of operations for data management in MDV Co. Ltd. are conducted in accordance with standard operational procedures of MDV Co. Ltd...

Data analysis will be conducted by Crecon Medical Assessment Inc. (Tokyo, Japan). The final results will be quality checked internally by Crecon Medical Assessment according to their internal procedures. For quality assurance of analysis, they will conduct code review of all modules of program, descriptive statistics review of all variables and patients row data examination of all output results in a test phase.

7.9. Limitations of the research methods

1) Identification of NVAF, bleeding, stroke, TIA and SE events will be based on insurance claims data, and there is no medical record review to adjudicate these diagnosis, which may subject the

study of misclassification bias. 2) There is no information about the therapeutic range of warfarin therapy or INR monitoring results, which are important factors related to the safety and efficacy of warfarin treatment. In Japan, it has been pointed out that coagulation status is often sub-optimally controlled by warfarin in NVAF patients. 3) This is an observational study and patients with different treatments may be incomparable. These differences may impact the comparison between treatment groups. In this study, a PSM method or IPTW with stabilized weights will be used to make well matched cohorts. Although the cohorts are matched, some differences in patient background which are neither available from the database nor included in matching score might still affect the results.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

The MDV database is comprised of unlinkable anonymized data. According to the ethical guidelines for epidemiological studies in Japan, informed consent is not always required for studies by unlinkable anonymized data.

8.2. Patient withdrawal

Not Applicable.

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Since the MDV database is comprised of unlinkable anonymized data, IRB/IEC approval is not required.

8.4. Ethical Conduct of the Study

Not Applicable.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study only includes data that already exist as structured data in an electronic database. In the data sources (MDV Co. Ltd.), it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and unprojected adverse events are not reportable as individual adverse event reports.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

All final data will be shared with BMSKK/BMS. It is also anticipated that results from this study will generate at least one study abstract for submission to a medical conference and one manuscript for submission to an international peer-reviewed journal. The appropriate conferences and journal will be decided upon by the alliance medical team. Abstract, presentation materials (poster or slide deck) or a manuscript will be reviewed and approved both by Pfizer and BMS

11. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

None.

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

None