CLINICAL STUDY PROTOCOL

Local, Multicenter, Phase II, Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients with Non-valvular Atrial Fibrillation

Protocol Number: LMI-2013-1013 (Triple AXEL)

Version: version 4.0

Date: 26 / Oct / 2015

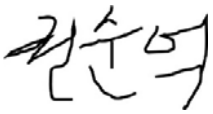
Confidential

Statement of Ethics: This study will be performed in accordance with Good Clinical Practice (GCP). Compliance with this standard means to guarantee public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki.

Signature Page

Protocol Number: LMI-2013-1013 (Triple AXEL)

I have fully reviewed the protocol and agree to comply with the procedures and contents provided in the protocol and ensure that this clinical study is carried out according to the International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Declaration of Helsinki, and ethical and legal regulations of the applicable area. I give my consent to keep confidential all the information developed or obtained in connection with this protocol.

Signature 	26 / Oct / 2015
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Clinical Study Protocol Synopsis

Study Title	Local, Multicenter, Phase II, Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients with Non-valvular Atrial Fibrillation
Protocol Number	LMI-2013-1013 (Triple AXEL)
Clinical Phase	Phase II (Investigator-Initiated Trial)
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Contract Research Organization	Clinical Research Center/Asan Medical Center Academic Research Office
Route of Administration of the Study Drug	Investigational product Study group: Bayer Xarelto tablet (10, 15, 20 mg) * Subcutaneous low dose heparin or LMWH can be used at the study doctor's discretion in order to prevent DVT, but it should be discontinued 24 hours before the dose of rivaroxaban.

	Control group: Daewha warfarin Tablet (2, 5 mg) (dosed concomitantly with Bayer Aspirin 100 mg QD from randomization day until the first results of INR > 1.7) * Subcutaneous low dose heparin or LMWH can be concomitantly used when INR is ≤ 1.7 at the study doctor's discretion in order to prevent DVT
Target Indication	Acute cerebral infarction or transient ischemic attack associated with non-valvular atrial fibrillation.
Study Duration	36 months from IRB approval date
Objectives	To assess the effects of warfarin or Xarelto (rivaroxaban) after four-week treatment (30 ± 5 days) in acute cerebral infarction or transient ischemic attack with nonvalvular atrial fibrillation based on the independent investigator's brain image interpretation. **Primary endpoint:** 1) To compare the incidence of intracranial bleeding or recurrent ischemic legions confirmed by the brain imaging (FLAIR/GRE, or SWI, or if necessary, DWI) after four-week (30 ± 5 days) treatment with Xarelto or warfarin between the two groups * Intracranial bleeding: symptomatic haemorrhage confirmed by CT or MRI or asymptomatic haemorrhage confirmed by GRE or SWI at Week 4 (30 ± 5 days) * Recurrent ischemic lesion: symptomatic cerebral infarction confirmed by the appropriate brain imaging or asymptomatic ischemic lesions confirmed by FLAIR at Week 4 (30 ± 5 days) **Secondary endpoints:** 1) the incidence of intracranial bleeding confirmed by brain imaging after 4 weeks treatment 2) the incidence of recurrent ischemic lesion confirmed by brain imaging after 4 weeks treatment 3) the total number of days of neurology division stay after randomization 4) the incidence of major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) - fatal bleeding: death due to bleeding within 30 days - Symptomatic haemorrhage which occurs in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, or intramuscular with compartment syndrome, retroperitoneal). - Overt bleeding causing a fall in haemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of red blood cell or whole blood 5) the incidence of acute artery syndrome (myocardial infarction or unstable angina) 6) the incidence of major vascular events: stroke, myocardial infarction, or vascular death (including bleeding and ischemic vascular events) 7) the incidence of major vascular events and major bleeding (defined by the ISTH) 8) the incidence of clinical ischemic events: recurrent cerebral infarction, myocardial infarction, other ischemic events requiring vascular intervention and ischemic vascular death 9) the difference between the two groups in a score of the mRS (modified Rankin scale) after 4 weeks treatment (30 ± 5 days)
Inclusion	1) Patients with acute ischemic stroke or transient ischemic attach presumed to be

Criteria	cardioembolic origin within 5 days from stroke onset (with mild severity: infarct size on DWI less than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, and 1/2 of one cerebellar hemisphere) 2) Patients with atrial fibrillation including paroxysmal atrial fibrillation: atrial fibrillation must be documented by ECG evidence within 30 days before randomization. This could be obtained from a notation in the subject's record (e.g., medical chart, hospital discharge summary). 3) Male or Female aged ≥19 years 4) Patients who voluntarily give their prior consent to participate in the study
Exclusion Criteria	1) Patients with chronic renal failure (CrCl < 30 ml/min) or severe hepatic impairment 2) Patients with significant haemorrhagic transformation: parenchymal hematoma type I or II by the ECASS definition 3) Patients with stroke presumed due to small vessel occlusion: single subcortical infarct in the perforating artery territory 4) Patients with large hemispheric or cerebellar infarction (larger than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, and 1/2 of one cerebellar hemisphere) 5) Patients who requires warfarin therapy due to replacement by prosthetic valve 6) Patients with active internal bleeding 7) Patients considered to have increased risk of bleeding due to a recent history of intracranial or intracerebral bleeding 8) Major surgery or major trauma within 30 days before screening that might be associated with increased bleeding risk 9) Clinically significant gastrointestinal bleeding within 6 months before screening 10) Intravenous tissue plasminogen activator(TPA) dosing or mechanical embolectomy within 48 hours before screening and 'significant haemorrhagic transformation as described above (exclusion criteria 2)' or 'cerebral hemisphere infarction or cerebellar infarction as described above (exclusion criteria 4)': patients achieving successful reperfusion without haemorrhage nor large infarction are eligible for enrollment 11) Severe anaemia: hemoglobin <10 g/dL 12) Bleeding diathesis; thrombocytopenia (<90,000/μL, prolonged PT (INR>1.7) 13) Sustained uncontrolled hypertension: SBP >180 mmHg or DBP >100 mmHg 14) Severe devastating illness, such as end-stage cancer, hepatic failure; therefore, patients with a life expectancy less than 6 months. 15) Patients with planned invasive procedure with potential for uncontrolled bleeding, including major surgery 16) The longer period out of 1 month before screening or 5 times of the half-lives of an active ingredients of CYP3A4 inhibitor or P-gp inhibitors, has not passed since the last administration of CYP3A4 and P-gp inhibitors that may increase significantly the pharmacodynamic effect of rivaroxaban or patients who are scheduled to take those medicines during this study: azole antifungal agents including ketoconazole, itraconazole, voriconazole, and posaconazole and HIV protease inhibitors including ritonavir. 17) The longer period out of 1 month before screening or 5 times of the half-lives of an active ingredients of CYP3A4 inducer or P-gp inducer has not passed since the last administration of CYP3A4 and P-gp inducers that may significantly decrease the

	pharmacodynamics effect of rivaroxaban or patients who are scheduled to take those medicines during this study: rifampicin /rifampin, phenytoin, phenobarbital, carbamazepine, and Saint. John's wort 18) Expected long-term use of NSAIDs 19) Drug or alcohol abuse 20) Patients in whom MRI is prohibited 21) Pregnant or lactating women 22) Patients who are allergic or hypersensitive to the investigational drugs (rivaroxaban, warfarin, and aspirin) or in whom the drugs are contradicted 23) Patients who cannot or are not willing to carry out the procedures required in this study 24) Patients who are investigators that are related directly to this study or employees of the center 25) Patients who are not willing to use contraception methods during this study 26) Patients who participated in another clinical study within 3 months before the first study drug dose or are participating in another clinical study (excluding observational studies; the end of a previous clinical study is defined as the last dosing date of the investigational product on previous study) 27) Patients considered ineligible for the study by the investigator due to other reasons including the results of laboratory test
Study Details and Study Methodology	**Study Details** 1) This is the exploratory phase II clinical study in acute cerebral infarction patients or transient ischemic attack patients with non-valvular atrial fibrillation. 2) The patients who are eligible at screening visit will be randomized to either the rivaroxaban group or warfarin group in a 1:1 ratio. 3) The primary objective of the rivaroxaban group and warfarin group is to compare the incidences of intracranial haemorrhage or recurrent ischemic legions between the two treatment groups based on the brain imaging (FLAIR/GRE, or SWI, or if necessary, DWI) results after 4 weeks (30 ± 5 days) of the first dose. 4) The secondary objectives of the rivaroxaban group and warfarin group are: - the incidence of intracranial haemorrhage confirmed by brain imaging at Week 4 - the incidence of ischemic legions confirmed by brain imaging at Week 4 - the total number of days of neurology division hospital stay after randomization - to compare the following occurrences from the first dose to Week 4 (30 ± 5 days) between two groups : the incidence of major bleeding : the incidence of acute artery syndrome (myocardial infarction or unstable angina) : the incidence of major vascular events : the incidences of major vascular events and major bleeding : the incidence of clinical ischemic events - to assess the difference between the two groups in the Modified Rankin Scale (mRS) scores **Study Methodology**

	Rivaroxaban group Rivaroxaban 10 mg will be dosed orally once daily from the randomization to Day 5 ± 2. In patients with the estimated CrCl ≥ 45 ml/min at screening, rivaroxaban 15 mg or 20 mg depending on the estimated CrCl at screening will be dosed from Day 6 ± 2 without a special renal function test. In patients with the estimated CrCl < 45 ml/min at screening, rivaroxaban 15 mg or 20 mg once daily depending on the renal function measured at Day 5 ± 2 will be dosed from Day 6 ± 2 to Week 4 (Day 30 ± 5). At Week 4 Visit, patients will have the tests including braining imaging, and can switch to the conventional treatment containing warfarin at the physician's discretion. For safe switch from rivaroxaban to warfarin, rivaroxaban is dosed concomitantly with warfarin for 5 days; after the concomitant use of rivaroxaban and warfarin is continued until the patients receive the safety tests including INR at the OPD after 7 ± 1 days of the last visit (Week 4) or INR becomes ≥ 2.0, it can be switched to warfarin alone. In the latter case, Week 5 Visit can be exempted. In case of continuous use of rivaroxaban after the study period, Week 5 Visit will not be carried out. At post-study visit (Day 44 ± 5), visit or phone monitoring will be carried out to check adverse events. **Warfarin group** After randomization, warfarin plus aspirin will be dosed concomitantly (for the subjects who are taking warfarin at randomization and has baseline INR >1.7, warfarin alone will be taken without aspirin). At Day 5 ± 2 days, INR will be checked; when INR > 1.7 is reached, aspirin will be stopped and warfarin alone will be taken. INR will be measured at Week 2 to verify whether the warfarin dose is well maintained, and, if necessary, the dose will be adjusted with a target at INR 2-3. The last dose of the investigational drug will be taken Week 4 (Day 30 ± 5), and the tests including brain imaging will be carried out at the OPD after the last dose of warfarin. Afterwards, warfarin, a conventional treatment, will be maintained. At post-study visit (Day 44 ± 5), visit or phone monitoring will be carried out to check adverse events.
Number of Trial Subjects	Warfarin group: 98 patients Rivaroxaban group: 98 patients **Rationale** This study is not for confirmatory validation of the effects of the two drugs but for exploratory verification to see whether the effects of rivaroxaban is equivalent to those of warfarin. In order to calculate the expected sample size with the 5% (one-sided) significance level and 80% power: 1) 89 subjects are required per group for hypothesis testing if it is assumed the incidence of intracranial bleeding or recurrent ischemic lesions is 25% and the least significant difference (LSD) is 15%; 2) 56 subjects are required for hypothesis testing if it is assumed the incidence of intracranial bleeding or recurrent ischemic lesions is 30% and the LSD is 20%. Considering dropout and inaccurate expected incidence of events due to a lack of previous studies, it is planned to recruit 98 subjects per group.
Evaluation method	**Pharmacodynamic Assessment** **Brain imaging (FLAIR/GRE or SWI or, if required, DWI):** at screening, Week 4, and at the investigator's discretion

	Modified Rankin Scale (mRS): at screening, Week 4 and at the investigator's discretion Safety Assessment **Vital sings (blood pressure and pulse)**: at screening, Week 4 and at the investigator's discretion **Laboratory tests:** Screening, Week 4: CBC, AST, ALT, Glucose, BUN, Serum Cr, PT, APTT, Na, K, Total Cholesterol, hs-CRP Day 5*, Week 2**: PT, BUN, Serum Cr Week 5 (applicable to the subjects who should carry out a visit in the rivaroxaban group): PT, BUN, serum Cr. and tests required at the investigator's discretion will be conducted. * Applicable to all warfarin groups; in case of the rivaroxaban group, the patients with CrCl ≥ 45ml/min at screening can skip the serum Cr test (the dose of rivaroxaban will be decided based on the result of CrCl at screening). ** Only applicable to the warfarin group **Electrocardiogram (12 lead ECG):** at screening **NIHSS:** at screening, Week 4 and at the investigator's discretion **Adverse events:** at the investigator's discretion, from the randomization day to the post-study visit
Analysis population	The analysis sets required to assess the efficacy and safety in this study will be compliant with the local and international standards. The efficacy analysis will include both the ITT and PP analysis sets as defined below; the safety analysis will be defined and carried out as below: **Modified intention to treat analysis set** The modified ITT is defined as all subjects randomized after giving the consent to participation in the study. However, the subjects who have never taken the investigational products (warfarin and rivaroxaban) or had no efficacy endpoints measured in the ITT set even after taking the investigational products will be excluded from the analysis. **Per protocol analysis set (optional)** The subjects in the modified ITT, who do not violate the inclusion/exclusion criteria and have rivaroxaban or warfarin compliance of≥80% will be included in the analysis. **Interim analysis** When a majority of subjects (100) have completed the study, the interim safety analysis will be carried out in order to determine whether or not to continue the study. The safety analysis will be done by an independent statistician. Then the steering committee will be commenced to have the final decision of continuity of the study based on the results of safety analysis. The efficacy analysis will be performed after the completion of the study.
Statistical Analysis	For all the variables used for this study, the frequency and proportion of categorical data will be presented, and the summary statistics of continuous data will be provided using the mean and standard deviation. The basic method for all statistical tests to be used for analyses will be two-sided tests except for the primary endpoints (the recurrent incidence of intracranial bleeding and ischemic lesions). The statistical significance will be tested at a 5% significance level, and, if necessary, a two-sided 95% confidence interval will be provided. If the variables are verified that show the difference between the groups after randomization including age and baseline test results except for efficacy and safety

	analyses, a regression model will be introduced which can adjust and analyse the risk or prognostic factors for endpoints.

Terms and Abbreviations

ACA	Anterior Cerebral Artery
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
CBC	Complete blood cell count
Cr	Creatinine
CrCl	Creatinine Clearance
CT	Computed tomography
CYP3A4	Cytochrome P 3A4
DBP	Diastolic blood pressure
DVT	Deep vein thrombosis
DWI	Diffusion weighted MRI
ECASS	European cooperative acute stoke study
ECG	Electrocardiogram
e-CRF	electronic Case Report Form
FLAIR	Fluid attenuated inversion recovery
GRE	Gradient Recalled Echo
HCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
hs-CRP	High sensitivity-C reactive protein
IIRC	Independent imaging review center
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intention to treat
IWRS	Interactive web response system
K	Potassium
LMWH	Low molecular weight heparin
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
Na	Sodium
NIHSS	National Institute of Health Stroke Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
P-gp	P-glycoprotein
PP	Per protocol
PT	Prothrombin time
SBP	Systolic blood pressure
SWI	Susceptibility Weighted Imaging
TPA	Tissue Plasminogen Activator
GLM	General Linear Model
GLMM	General Linear Mixed Model

40 **Study Flow Chart**

Activities	Screening (from Day -5)	Baseline (Day 1)	Day 5 ± 2	Week2 (Day 14 ± 5)	Week 4 (Day 30 ± 5)	Week 5 (Week 4 Visit + 7±1 days)	Post study visit[1]	Unscheduled visit[2]
Informed consent	●							
Basic demographics	●							
Inclusion/exclusion criteria	●	●						
Medical history	●							
Vital signs	●				●			●
Laboratory test[3]	●		●	●[4]	●	●[5]		●
Pregnancy Test[6]	●							
Electrocardiogram	●							
Brain imaging[7]	●				●			●
mRS	●				●			●
NIHSS	●				●			●
HAS-BLED, CHADS2-VASC		●						
Randomization[8]		●						
Administration of study drug[9]		→	→	→	→	→		
Medication compliance		●	●	●[4]	●			
Adverse event		→	→	→	→	→	→	●
Concomitant medications	●	→	→	→	→	●[5]		●

[1] It can be replaced by phone contact monitoring (44 ± 5 days).
[2] The test is conducted for the items required at the investigator's discretion.
[3] Screening and Week 4: all items of CBC, AST, ALT, BUN, Cr, PT, APTT, Na, K, Total cholesterol, and hs-CRP. For screening visit, measurements in the E.R. before obtaining the consent can be used instead; At Day 5 PT, BUN, and Cr will be measured (applicable to all in the warfarin group; For the rivaroxaban group, the serum Cr. test can be skipped in patients with CrCl ≥ 45ml/min measured at screening), Week 2: only applicable to the warfarin group; PT, BUN, Cr, Week 5: only applicable to the rivaroxaban; PT, BUN, Cr
[4] Only applicable to the warfarin group
[5] Applicable to certain patients in the warfarin group (Week 5 Visit is scheduled 7±1 days after Week 4)
[6] For women of childbearing potential, HCG urine test
[7] At screening, any test result measured in the E.R. before the consent is obtained can be used instead. At Week 4, it will be measured.
[8] Randomization is possible at screening on the assumption that all scheduled tests have been carried out (However, the study will be conducted with the first dose day of the investigational product considered as Day 1).
[9] In the rivaroxaban group, concomitant use of warfarin and rivaroxaban will continue for 5 days after switch to warfarin.

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1 Study Title and Phase

Local, Multicenter, Phase II, Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and hospital stay in Acute Cerebral Infarction Patients with Nonvalvular Atrial Fibrillation

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3 Study Objective and Background

3.1 Study Objective

To assess the effects of warfarin or Xarelto (rivaroxaban) after four-week treatment (30 ± 5 days) in acute cerebral infarction or transient ischemic attack with nonvalvular atrial fibrillation based on the independent investigator's brain image interpretation.

Primary endpoint:

1. To compare the incidence of intracranial bleeding or recurrent ischemic legions confirmed by the brain imaging (FLAIR/GRE, or SWI, or if necessary, DWI) after four-week (30 ± 5 days) treatment with Xarelto or warfarin between the two groups

* Intracranial bleeding: symptomatic haemorrhage confirmed by CT or MRI or asymptomatic haemorrhage confirmed by GRE or SWI at Week 4 (30 ± 5 days)

* Recurrent ischemic lesion: symptomatic cerebral infarction confirmed by the appropriate brain imaging or asymptomatic ischemic lesions confirmed by FLAIR at Week 4 (30 ± 5 days)

Secondary endpoints:

1. the incidence of intracranial bleeding confirmed by brain imaging after 4 weeks treatment
2. the incidence of recurrent ischemic lesion confirmed by brain imaging after 4 weeks treatment
3. the total number of days of neurology division stay after randomization
4. the incidence of major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH)
   - fatal bleeding: death due to bleeding within 30 days
   - Symptomatic haemorrhage which occurs in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, or intramuscular with compartment syndrome, retroperitoneal).
   - Overt bleeding causing a fall in haemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of red blood cell or whole blood
5. the incidence of acute artery syndrome (myocardial infarction or unstable angina)
6. the incidence of major vascular events: stroke, myocardial infarction, or vascular death (including bleeding and ischemic vascular events)
7. the incidence of major vascular events and major bleeding (defined by the ISTH)
8. the incidence of clinical ischemic events: recurrent cerebral infarction, myocardial infarction, other ischemic events requiring vascular intervention and ischemic vascular death
9. the difference between the two groups in a score of the mRS (modified Rankin scale) after 4 weeks treatment (30 ± 5 days)

3.2 Study Background

Atrial fibrillation is one of the major causes of cerebral infraction[1], and about 20 % of patients with cerebral infarction have atrial fibrillation in Korea.[2] Atrial fibrillation tends to increase in proportion to the age, and patients with cerebral infarction associated with atrial fibrillation are consistently on the rise worldwide.[3] Patients with cerebral infarction associated with atrial fibrillation have a high risk of recurrent stroke, requiring aggressive treatment strategies to prevent cerebral infarction. Many clinical trials have demonstrated that aspirin reduced the risk of stroke by 20%, and some have reported oral anticoagulants decreased the risk of recurrent stroke by over 66%. As patients especially with cerebral infraction have higher risk of recurrent stroke associated with atrial fibrillation, it is recommended to use warfarin in patients with cerebral infarction associated with atrial fibrillation.[4-6]

Risk of recurrent cerebral infarction is higher within the first month of cerebral infarction associated with atrial fibrillation.[7] Therefore, it is desirable to carry out anticoagulant therapy in patients with acute cerebral infarction. However, warfarin, a widely-used oral anticoagulant, causes the transient hypercoagulable state in the early phase of treatment, increasing the risk of ischemic events including embolism; it takes 4 to 5 days to have an adequate anticoagulant effect. In order to reduce such risk, the studies dosing heparin or low molecular weight-heparin in patients with acute cerebral infarction were carried out.[8, 9] However, they didn't show the improvement in prognosis compared than the non-treatment group due to major bleeding events such as an increase in haemorrhagic transformation due to reopened blood vessel in infarcted tissues or intracranial haemorrhage. Based on these clinical study results, the guidelines on stroke treatment in most countries including Korea and the US cannot recommend an anticoagulant therapy in acute stroke patients.[10,11]

The current treatment guideline for acute cerebral infarction patients with atrial fibrillation is to dose aspirin and warfarin concomitantly after dosing aspirin alone for a certain period[12] and discontinue aspirin to use

warfarin alone at the first time when INR value, which can indicate an anticoagulant effect by warfarin, exceeds 1.7. However, there is no proper recommendation about an appropriate time to dose warfarin.

Dosing of aspirin and warfarin in acute cerebral infarction patients with atrial fibrillation in accordance with the current treatment guideline may cause the increased risk of ischemia due to transient hypercoagulable state that may occur in the initial phase of treatment with warfarin[16] and increased risk of bleeding associated with excessive anticoagulation, and unavoidably frequent blood tests and prolonged hospitalization due to unknown time of anticoagulant effect by warfarin. It may also increase the risk of bleeding associated with aspirin concomitantly used in the initial phase of treatment.

Rivaroxaban is a newly developed factor Xa inhibitor, a new oral anticoagulant. A recent large-scale clinical trial in patients at high risk of stroke and atrial fibrillation showed that rivaroxaban reduced cardiovascular events significantly including stroke compared to warfarin.[13] The drug is commonly used to prevent stroke in patients at high risk of stroke with atrial fibrillation because it is more convenient to take than warfarin, and decreased significantly the incidence of intracranial bleeding in the clinical trial in these high-risk patients.[13, 14]

Considering these excellent results from clinical trials as well as the rapid onset of action and consistent effects, rivaroxaban is expected to be a good alternative in patients with acute cerebral infarction.

Rivaroxaban, unlike warfarin, does not lead to a transient hypercoagulable state in the initial phase of treatment and may reduce the risk of ischemic events. Rivaroxaban does not cause excessive anticoagulation which may occur in the initial phase of treatment with warfarin, and can reduce the incidence of bleeding caused by aspirin and shorten hospital stay.

The clinical study Triple AXEL will evaluate the incidence of ischemia and bleeding as adverse events, and hospital stay by rivaroxaban, a new oral anticoagulant compared to the conventional treatment and assess if rivaroxaban can be a new treatment guide in patients with acute cerebral infarction associated with atrial fibrillation.

4 Trial Design and Rationale

Randomized, active comparator, open-label clinical trial

Rivaroxaban group

Rivaroxaban 10 mg will be dosed orally once daily from the randomization to Day 5 ± 2. In patients with the estimated CrCl ≥ 45 ml/min at screening, rivaroxaban 15 mg or 20 mg depending on the estimated CrCl at screening will be dosed from Day 6 ± 2 without a special renal function test. In patients with the estimated CrCl < 45 ml/min at screening, rivaroxaban 15 mg or 20 mg once daily depending on the renal function measured at Day 5 ± 2 will be dosed from Day 6 ± 2 to Week 4 (Day 30 ± 5). At Week 4 Visit, patients will have the tests including braining imaging, and can switch to the conventional treatment containing warfarin at the physician's discretion. For safe switch from rivaroxaban to warfarin, rivaroxaban is dosed concomitantly with warfarin for 5 days; after the concomitant use of rivaroxaban and warfarin is continued until the patients receive the safety tests including INR at the OPD after 7 ± 1 days of the last visit (Week 4) or INR becomes ≥ 2.0, it can be switched to warfarin alone. In the latter case, Week 5 Visit can be exempted. In case of continuous use of rivaroxaban after the study period, Week 5 Visit will not be carried out. At post-study visit (Day 44 ± 5), visit or phone monitoring will be carried out to check adverse events.

Warfarin group

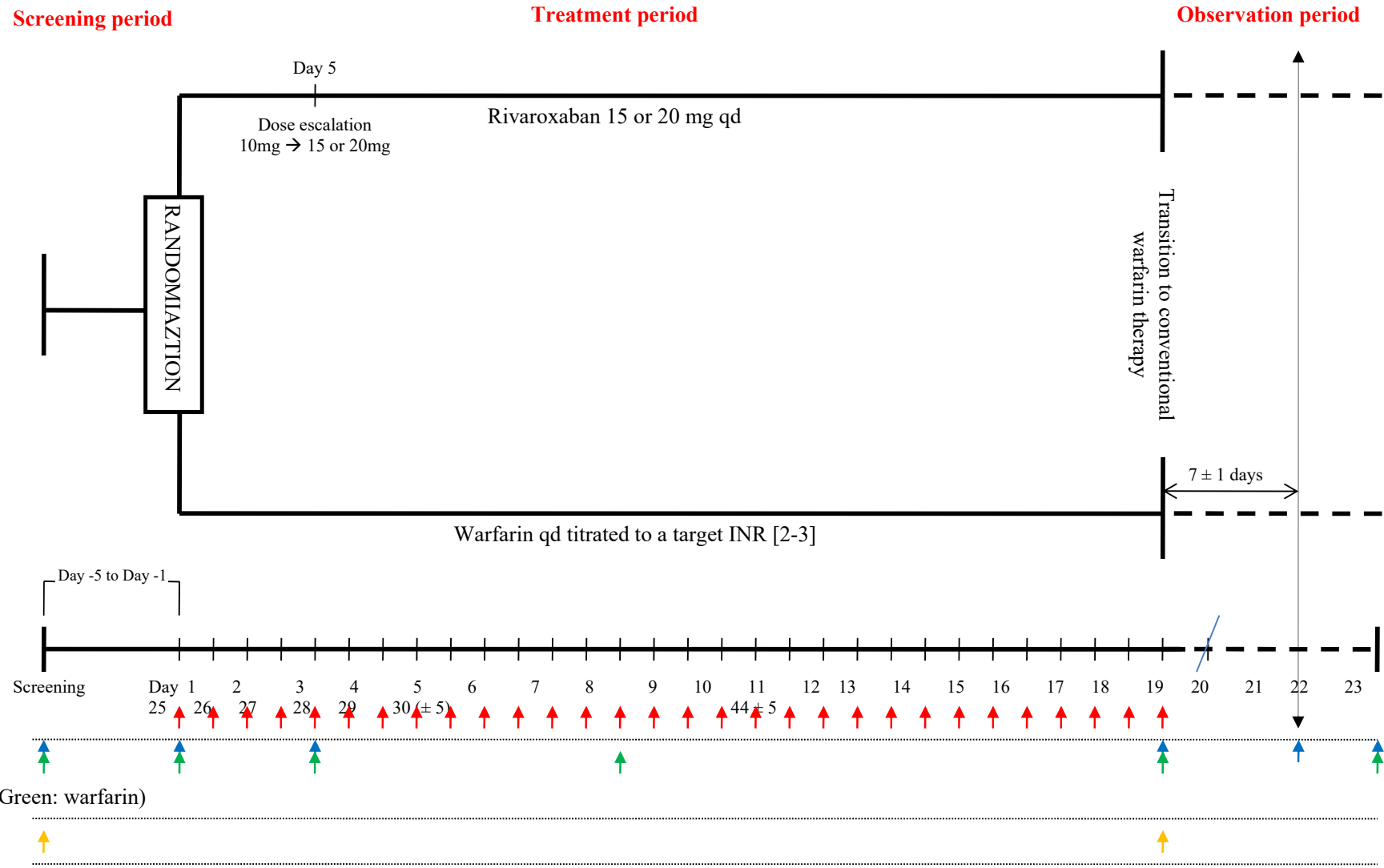
After randomization, warfarin plus aspirin will be dosed concomitantly (for the subjects who are taking warfarin at randomization and has baseline INR >1.7, warfarin alone will be taken without aspirin). At Day 5 ± 2 days, INR will be checked; when INR > 1.7 is reached, aspirin will be stopped and warfarin alone will be taken. INR will be measured at Week 2 to verify whether the warfarin dose is well maintained, and, if necessary, the dose will be adjusted with a target at INR 2-3. The last dose of the investigational drug will be taken Week 4 (Day 30 ± 5), and the tests including brain imaging will be carried out at the OPD after the last dose of warfarin. Afterwards, warfarin, a

conventional treatment, will be maintained. At post-study visit (Day 44 ± 5), visit or phone monitoring will be carried out to check adverse events.

The conventional treatment guideline for acute cerebral infarction patients with atrial fibrillation is to dose aspirin plus warfarin concomitantly[12] and to stop aspirin and begin warfarin alone when INR, which assesses the anticoagulant effect of warfarin, starts to exceed 1.7.

The control group is designed to begin with aspirin plus warfarin at randomization, and, when INR >1.7 reached, warfarin QD alone with a target at INR 2-3 (in case that patients who have been given warfarin before participating in the study and their baseline INR exceeds 1.7, warfarin alone, not in combination with aspirin, may be dosed with a target at INR 2-3).

Rivaroxaban, a factor Xa inhibitor, reduced significantly the incidence of cardiovascular events including stroke compared to warfarin in a large-scale clinical trial involving patients at high risk of stroke with atrial fibrillation.[13] This clinical trial is designed to dose rivaroxaban 10 mg for the first 5 ± 2 days after randomization, and then rivaroxaban 15 mg or 20 mg depending on the renal function.


Screening period
Treatment period
Observation period
Day 5
Dose escalation
10mg → 15 or 20mg
Rivaroxaban 15 or 20 mg qd
RANDOMIAZTION
Transition to conventional warfarin therapy
7 ± 1 days
Warfarin qd titrated to a target INR [2-3]
Day -5 to Day -1
Screening
Day 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
25
26
27
28
29
30 (± 5)
44 ± 5
Drug administration
Visit
(Blue; rivaroxaban, Green: warfarin)
Brain image

5 Planned Study Duration

36 months from IRB approval date

: The period of treatment with the investigational product is from randomization to Week 4 (30 ± 5). For treatment thereafter, switch to the conventional standard treatment will be performed at the physician's discretion. However, the safety information will be collected until 44 ± 5 days during the post-study visit, and reported to the regulatory authorities in compliance with the relevant regulations.

6 Target Disease

Acute cerebral infarction or transient ischemic attack associated with non-valvular atrial fibrillation.

7 Inclusion/exclusion Criteria

7.1 Inclusion Criteria

1. Patients with acute ischemic stroke or transient ischemic attach presumed to be cardioembolic origin within 5 days from stroke onset (with mild severity: infarct size on DWI less than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, and 1/2 of one cerebellar hemisphere)
2. Patients with atrial fibrillation including paroxysmal atrial fibrillation: atrial fibrillation must be documented by ECG evidence within 30 days before randomization. This could be obtained from a notation in the subject's record (e.g., medical chart, hospital discharge summary).
3. Male or Female aged ≥19 years
4. Patients who voluntarily give their prior consent to participate in the study

7.2 Exclusion Criteria

1. Patients with chronic renal failure (CrCl < 30 ml/min) or severe hepatic impairment
2. Patients with significant haemorrhagic transformation: parenchymal hematoma type I or II by the ECASS definition
3. Patients with stroke presumed due to small vessel occlusion: single subcortical infarct in the perforating artery territory
4. Patients with large hemispheric or cerebellar infarction (larger than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory, and 1/2 of one cerebellar hemisphere)
5. Patients who requires warfarin therapy due to replacement by prosthetic valve
5. Patients with active internal bleeding
6. Patients considered to have increased risk of bleeding due to a recent history of intracranial or intracerebral bleeding
7. Major surgery or major trauma within 30 days before screening that might be associated with increased bleeding risk
8. Clinically significant gastrointestinal bleeding within 6 months before screening
9. Intravenous tissue plasminogen activator(TPA) dosing or mechanical embolectomy within 48 hours before screening and 'significant haemorrhagic transformation as described above (exclusion criteria 2)' or 'cerebral hemisphere infarction or cerebellar infarction as described above (exclusion criteria 4)': patients achieving successful reperfusion without haemorrhage nor large infarction are eligible for enrollment
10. Severe anaemia: hemoglobin <10 g/dL
11. Bleeding diathesis; thrombocytopenia (<90,000/μL, prolonged PT (INR>1.7)

12. Sustained uncontrolled hypertension: SBP >180 mmHg or DBP >100 mmHg
13. Severe devastating illness, such as end-stage cancer, hepatic failure; therefore, patients with a life expectancy less than 6 months.
14. Patients with planned invasive procedure with potential for uncontrolled bleeding, including major surgery
15. The longer period out of 1 month before screening or 5 times of the half-lives of an active ingredients of CYP3A4 inhibitor or P-gp inhibitors, has not passed since the last administration of CYP3A4 and P-gp inhibitors that may increase significantly the pharmacodynamic effect of rivaroxaban or patients who are scheduled to take those medicines during this study: azole antifungal agents including ketoconazole, itraconazole, voriconazole, and posaconazole and HIV protease inhibitors including ritonavir.
16. The longer period out of 1 month before screening or 5 times of the half-lives of an active ingredients of CYP3A4 inducer or P-gp inducer has not passed since the last administration of CYP3A4 and P-gp inducers that may significantly decrease the pharmacodynamics effect of rivaroxaban or patients who are scheduled to take those medicines during this study: rifampicin /rifampin, phenytoin, phenobarbital, carbamazepine, and Saint. John's wort
17. Expected long-term use of NSAIDs
18. Drug or alcohol abuse
19. Patients in whom MRI is prohibited
20. Pregnant or lactating women
21. Patients who are allergic or hypersensitive to the investigational drugs (rivaroxaban, warfarin, and aspirin) or in whom the drugs are contradicted
22. Patients who cannot or are not willing to carry out the procedures required in this study
23. Patients who are investigators that are related directly to this study or employees of the center
24. Patients who are not willing to use contraception methods during this study
25. Patients who participated in another clinical study within 3 months before the first study drug dose or are participating in another clinical study (excluding observational studies; the end of a previous clinical study is defined as the last dosing date of the investigational product on previous study)
26. Patients considered ineligible for the study by the investigator due to other reasons including the results of laboratory test

8 Details and Methods of Clinical Study

8.1 Selection of Control Group for Comparison

Control group	Study group
Daewha warfarin Tablet (2, 5 mg) *concomitant dosing with aspirin until the first results of INR **> 1.7**	Bayer Xarelto tablet (10, 15, 20 mg)
Subcutaneous low dose heparin or LMWH can be concomitantly used when INR is ≤ 1.7 at the study doctor's discretion in order to prevent DVT	Subcutaneous low dose heparin or LMWH can be used at the study doctor's discretion in order to prevent DVT, but it should be discontinued 24 hours before the dose of rivaroxaban.

8.2 Randomization and Blinding

All subjects who meet the inclusion criteria and do not fall under the exclusion criteria will be randomized to either the study group (rivaroxaban) or control group (warfarin) in a 1:1 ratio.

Randomization method: The randomization table is prepared and linked to an e-CRF. The subjects assessed eligible at the screening test are block-randomized to one of two treatment groups in order of enrolment using the interactive web response system (IWRS). This is an open-label study where both the investigators and patients are aware of assigned treatment.

Treatment group	No. of subjects	Dosage and administration	Route of administration
Control group	98	Concomitant administration of aspirin 100 mg once daily and warfarin once daily 3) INR > 1.7 Warfarin once daily with a target at INR 2-3	per oral
Study group	98	Rivaroxaban 10 mg once daily for 5 ± 2 days Day 6 ± 2 : Rivaroxaban 15 mg or 20 mg once daily depending on the patient's CrCl - CrCl 30-49 m/min: 15 mg, once a day - CrCl ≥ 50 ml/min: 20 mg, once a day	per oral

8.3 Study Assessment, Observation Timepoint and Method

8.3.1 Study Assessment, Observation Timepoint and Method

1. Screening (- 5 day to -1 day)

- ✓ Explanation of Subject Information Sheet and Collection of voluntarily signed consent form
- ✓ Review and verification of the inclusion and exclusion criteria
- ✓ Subject basic information (demographic information: date of birth, age, gender, height and weight) and medical history
- ✓ Vital sign measurement (systolic/diastolic blood pressure and pulse)
- ✓ Laboratory tests (all items of CBC, AST/ALT, BUN, Cr, PT, APTT, Na, K, Total cholesterol, and hs-CRP; Any result of tests conducted at E.R. before subject consent obtainment can be used instead of new testing.)
- ✓ Urine HCG for women of childbearing potential
- ✓ 12 lead ECG (Any result of ECG conducted at E.R. before subject consent obtainment can be used instead.)
- ✓ Brain imaging (FLAIR/GRE or SWI/DWI)
  (Any result of CT and/or MRI carried out at E.R. before subject consent obtainment can be used instead.)
- ✓ Investigations on concomitant medications
- ✓ mRS and NIHSS assessment

2. Baseline (Day 1; the first dosing date of investigational product)

- ✓ Review and verification of the inclusion and exclusion criteria

- ✓ Randomization to the control group or treatment group
- ✓ Administration of the investigational product
- ✓ Adverse event monitoring
- ✓ Investigations on concomitant medication
- ✓ Drug compliance
- ✓ HAS-BLED and CHADS2-VASC

3. Day 5 (Day 5 ± 2)

- ✓ Laboratory tests (PT, BUN, Cr)

* Applicable to all warfarin groups; in case of the rivaroxaban group, the patients with CrCl ≥ 45ml/min at screening can skip the serum Cr test (the dose of rivaroxaban will be decided based on the result of CrCl at screening).

- ✓ In the rivaroxaban group, the dose will be adjusted based on CrCl before administration. In the warfarin group, aspirin will be discontinued based on INR result. If required, the dose of warfarin is adjusted before administration.
- ✓ Drug compliance
- ✓ Adverse event monitoring
- ✓ Investigations on concomitant medication

4. Only for warfarin group; Day 14 ± 5 (Week 2)

- ✓ Laboratory tests (PT, BUN, Cr)
- ✓ Checking the adequate warfarin dose, and, if necessary, dose adjustment before administration
- ✓ Drug compliance
- ✓ Adverse event monitoring
- ✓ Investigations on concomitant medication

5. Day 30 ± 5 (Week 4)

- ✓ Vital sign measurement (systolic/diastolic blood pressure and pulse)
- ✓ Laboratory tests (all items of CBC, AST/ALT, BUN, Cr, PT, APTT, Na, K, Total cholesterol, and hs-CRP)
- ✓ Brain imaging (FLAIR/GRE or SWI or, if necessary, DWI)
- ✓ NIHSS and mRS assessment
- ✓ Drug compliance
- ✓ Adverse event monitoring
- ✓ Investigations on concomitant medication
- ✓ Last dosing of the investigational product. Afterwards, the treatment will be switched to the currently common treatment or maintained at the physician's discretion (For safe switch from rivaroxaban to warfarin, the quantities for 5-day dosings of rivaroxaban will be dispensed so that rivaroxaban can be concomitantly used with warfarin for 5 days. If a subject in rivaroxaban continues rivaroxaban at physician's discretion or concomitant dosing of rivaroxaban and warfarin is used until INR≥2.0 and then switched to warfarin alone, Week 5 Visit can be skipped.)
- ✓ Total number of days of neurology division stay from randomization will be checked and recorded.

6. A part of patients in rivaroxaban group; 7± 1 days after Week 4 Visit (Week 5)

- ✓ Laboratory tests (PT, BUN, Cr)
- ✓ Adverse event monitoring

✓ concomitant medication monitoring

7. Post study visit (Day 44 ± 5)

✓ Adverse event monitoring

8. Unscheduled Visit

If the subject visits the hospital relating to an adverse event apart from scheduled visits during the study, his/her status should be checked by the following tests and assessments at the investigator's discretion. The data related to all the adverse events occurring from randomization and the last visit (Day 44 ± 5) should be recorded in source documents and CRFs in an accurate and complete way. When subjects visits a study center for other purposes, tests and assessment will not be conducted.

✓ Vital signs (systolic/diastolic blood pressure and pulse) measurement

✓ Laboratory tests required at the investigator's discretion

✓ Brain imaging (CT or MRI) at the investigator's discretion

✓ NIHSS and mRS assessment at the investigator's discretion

✓ Adverse event monitoring

✓ Concomitant medications investigation

Activities	Screening (from Day -5)	Baseline (Day 1)	Day 5 ± 2	Week 2 (Day 14 ± 5)	Week 4 (Day 30 ± 5)	Week 5 (Week 4 Visit + 7±1 days)	Post study visit[1]	Unscheduled visit[2]
Informed consent	●							
Basic demographics	●							
Inclusion/exclusion criteria	●	●						
Medical history	●							
Vital signs	●				●			●
Laboratory test[3]	●		●	●[4]	●	●[5]		●
Pregnancy Test[6]	●							
Electrocardiogram	●							
Brain imaging[7]	●				●			●
mRS	●				●			●
NIHSS	●				●			●
HAS-BLED, CHADS2-VASC		●						
Randomization[8]		●						
Administration of study drug[9]		→	→	→	→	→		
Medication compliance		●	●	●[4]	●			
Adverse event		→	→	→	→	→	→	●
Concomitant medications	●	→	→	→	→	●[5]		●

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[1] It can be replaced by phone contact monitoring (44 ± 5 days).

[2] The test is conducted for the items required at the investigator's discretion.

[3] Screening and Week 4: all items of CBC, AST, ALT, BUN, Cr, PT, APTT, Na, K, Total cholesterol, and hs-CRP. For screening visit, measurements in the E.R. before obtaining the consent can be used instead; At Day 5 PT, BUN, and Cr will be measured (applicable to all in the warfarin group; For the rivaroxaban group, the serum Cr. test can be skipped in patients with CrCl ≥ 45ml/min measured at screening), Week 2: only applicable to the warfarin group; PT, BUN, Cr, Week 5: only applicable to the rivaroxaban; PT, BUN, Cr

[4] Only applicable to the warfarin group.

[5] Applicable to certain patients in the warfarin group (Week 5 Visit is scheduled 7±1 days after Week 4)

[6] For women of childbearing potential, HCG urine test

[7] At screening, any test result measured in the E.R. before the consent is obtained can be used instead. At Week 4, it will be measured.

[8] Randomization is possible at screening on the assumption that all scheduled tests have been carried out (However, the study will be conducted with the first dose day of the investigational product considered as Day 1).

[9] In the rivaroxaban group, concomitant use of warfarin and rivaroxaban will continue for 5 days after switch to warfarin.

8.3.2 Assessment Measures and Recording Methods

1. Brain imaging, mRS scores, NIHSS and laboratory tests

- Brain imaging

Brain imaging such as CT or MRI can be taken in accordance with each center's standard operating procedure (SOP). Braining imaging including GRE or SWI/FLAIRE or, if required, DWI should be carried out. The brain imaging data will be collected in the designated central Internet-based system and interpreted by the independent imaging review committee (IIRC). The IIRC may request data supplementation and each center should do its best to reply to the supplementation request.

- Modified Rankin Scale (mRS)

MRS (modified ranking scale) is a scale used to measure the degree of disability after onset of stroke. The scale runs from 0 to 6: 0 means no disability at all and a higher score indicates a severer disability. MRS to be used in this study is described in [Appendix 1].

- National institute of health stroke scale (NIHSS)

NIHSS is a tool to assess severity of neurological deficits. A higher score means a higher severity. NIHSS to be used in this study is described in [Appendix 2].

2. Laboratory tests

The laboratory tests will be carried out by the laboratory medicine division of each center, and the quality assurance certificate will be retained to guarantee reliability of the center's test results. The normal ranges of test results will be prepared, signed by the investigator and retained. They should be appropriately modified whenever the normal ranges of tests results are changed.

3. Adverse events

- All adverse events occurring during the study should be recorded, if possible, using the MedDRA preferred terms (PT). If this is not feasible, the used terms of the symptoms and signs observed by the investigator or reported by the subject will be recorded. In the CRF, symptoms and signs, duration (start and end dates), and severity (mile, moderate, and severe) of the adverse event, causal relationship with the study drug, action taken regarding the adverse event, serious adverse event (yes/no) will be recorded.

4. Subject demographic information and medical history

- The subject demographic information including date of birth, gender, and age will be checked, and his/her past and recent medical history and drug history will be verified through the inquiry. Also, the height (marked in three digits by rounding off to the nearest whole number, cm) and weight (rounded off to the nearest tenth, kg).

5. CrCl will be calculated with the Cockcroft Gault formula.

6. Standardization tool for warfarin dose

The loading dose of warfarin will be determined by the formula below to standardise the warfarin dose. The dose thereafter will be determined at the investigator's medical discretion.

Initial dose = exp [0.613 + (0.425 x BSA) - (0.0075 x age) + (0.156 x 0; Korean) + (0.216 x target INR) - (0.257 x amiodarone) + (0.108 x smokes) + 0.0784 x DVT/PE]

(Weight) $kg^{0.425}$ x (Height) $cm^{0.725}$ x 0.007184 = BSA in M^2

For the rivaroxaban group, the maintenance dose will be basically used without the loading dose considering bleeding risk when rivaroxaban is switched to warfarin at Week 4

7. Assessment Tools for Bleeding Risk

- HAS BLED Score

The HAS BLED score is a tool to assess bleeding risk with hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INRs, elderly, and drugs/alcohol usage. For

more details of the HAS BLED Score Calculator, a tool to be used in this study, see http://www.globalrph.com/has-bled-score.htm.

- CHADS2-VASC

This tool assesses the risk of ischemic stroke in patients with atrial fibrillation using congestive heart failure, hypertension, age (≥75), diabetes mellitus, stroke, vascular disease, age(65 -74), and sex category. For more details of CHADS2-VASC calculator, see http://clincalc.com/Cardiology/Stroke/CHADSVASC.aspx.

9 Investigational Products

Principal investigator and those who are entrusted with the duty by the principal investigator are responsible for investigational product management during this study.

9.1 Investigational Product Management and Recording

The investigational product managing pharmacist ("managing pharmacist") or a person who has been entrusted with the duty by the principal investigator ("a person designated by the principal investigator") will be responsible for managing and retrieving the drugs used in this study.

The study pharmacist or a person designated by the principal investigator should appropriately manage the investigational products according to the protocol and ensure that the investigational products are used in the subjects according to the protocol. The medical guidance will be provided for the subjects. When the subject visits the center, the investigational product purchase receipts and returned quantity for each randomized group will be collected and recorded. The returned investigational products should be stored in a safe cabinet or dedicated room that can be accessed only to the center staff. The unused investigational products will be stored until the sponsor makes a decision on the destruction or retrieval. If the study is completed, all unused drugs and a copy of the drug management record should be submitted to the monitor or destroyed according to the legal procedures.

9.2 Adverse Events

9.2.1 Rivaroxaban

System organ class	Common	Uncommon	Rare
Blood and lymphatic system disorders	Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]	
Cardiac disorders		Tachycardia	
Eye disorders	Eye haemorrhage (incl. conjunctival haemorrhage)		
Gastrointestinal disorders	Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth	
General disorders and administration site conditions	Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]
Hepatobiliary disorders		Hepatic function Abnormal	Jaundice
Immune system disorders		Allergic reaction, dermatitis allergic	

Injury, poisoning and procedural complications	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion	wound secretion[A]	Vascular pseudoaneurysm[C]
Investigations	Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal and connective tissue disorders	Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage
Nervous system disorders	Dizziness, headache Cerebral	Cerebral and intracranial haemorrhage, syncope	
Renal and urinary disorders	Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]		
Respiratory, thoracic and mediastinal disorders	Epistaxis, haemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria	
Vascular disorders	Hypotension, haematoma		

A: observed in prevention of venous thromboembolism (VTE) after major orthopedic surgery of the lower extremities

B: observed as very common in treatment of DVT and PE and decrease in recurrence risk in women < 55 years

C: observed as uncommon in prevention of acute coronary syndrome in patients following percutaneous coronary intervention)

9.2.2 Warfarin

1) Hematology System

(1) fatal or nonfatal hemorrhage from any tissue or organ: Bleeding caused by an overdose, bleeding of gastrointestinal and genitourinary tracts due to latent lesions, paralytic ileus and visceral disorder caused by submucous and intramural bleeding, excessive uterine bleeding, and haemorrhagic necrosis of women's breasts and other sites (necrosis, angiitis, and bleeding from skin and intra-skin tissues due to thrombosis), or adrenal hemorrhage may occur.

(2) Haemorrhagic complications may present as paralysis; paresthesia; headache, chest pain, abdominal pain, joint pain, muscle pain or other pain; dizziness; shortness of breath, difficulty in breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock.

(3) Leukopenia may occur.

2) Whole body: Rarely hypersensitivity/allergic reactions, pain, oedema, asthenia, fever, headache, fatigue, lethargy and malaise may occur.

3) CNS & PNS: Rarely dizziness and cold intolerance including feeling cold and chills may occur.

4) Gastrointestinal: Rarely nausea, diarrhea, vomiting, abdominal pain including cramping, and bloating may occur.

5) Liver and biliary system: Rarely elevated liver enzymes, hepatitis, jaundice, and cholestatic hepatic injury may occur.

6) Skin and skin appendage: Necrosis of skin and other tissues, and rarely alopecia, rash, pruritus, urticarial, and dermatitis including bullous eruptions may occur.

7) Vascular: Rarely systemic cholesterol micro-embolization, purple toes syndrome, and vasculitis may occur.

8) Sensory: Paresthesia, and rarely taste perversion may occur.

9) Long-term use: events of tracheal or tracheobronchial calcification in association with long-term therapy may occur.

10) Miscellaneous: Priapism may occur.

9.2.3 Aspirin

The listed adverse drug reactions are based on post-marketing spontaneous reporting for all oral aspirin agents including long- and short-term use.

1) Shock: Shock and anaphylactic shock (dyspnea, generalised flush, angioedema, and urticaria) may occur. Patients should be closely monitored, and if there is any abnormality, the medicinal product should be discontinued and proper action should be taken. This medicinal product may induce asthma attacks.

2) Hypersensitivity: Hypersensitivities including erythema, pruritus, nasal obstruction, cardiorespiratory disorders, sometimes rash, oedema, urticaria, rhinitis-like symptoms, and conjunctivitis may occur. In this case, the medicinal product should be discontinued.

3) Skin: Rare Lyell Syndrome (toxic epidermal necrolysis), Stevens-Johnson syndrome (mucocutaneous ocular syndrome) and exfoliative dermatitis may occur. Patients should be closely observed, and if there is any abnormality, the medicinal product should be discontinued and proper action should be taken.

4) Blood: Rarely aplastic anaemia, anaemia, leukopenia, thrombocytopenia, platelet dysfunction (prolonged bleeding time) may occur. Patients should be closely observed, and if there is any abnormality, the medicinal product should be discontinued and proper action should be taken. Hemolysis and hemolytic anaemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency has been reported.

5) Gastrointestinal: Anorexia, heartburn, stomachache, nausea and vomiting may occur. Long-term use may induce gastrointestinal events, especially gastrointestinal bleeding, peptic ulcer, and abreaction (perforation).

6) Psycho-neurotic: Tinnitus, hearing loss, dizziness, headache, and excitement may occur. If any of these symptoms occurs, the dose should be reduced or the medicinal product should be discontinued.

7) Liver: Rarely hepatic impairment may occur. Transient hepatic impairment with increase in liver transaminases has very rarely been reported.

8) Kidney: Renal impairment and acute renal failure have been reported.

9) Miscellaneous: Hyperpnea or metabolic acidosis may significantly increase the blood levels. The dose should be reduced or the medicinal product should be discontinued.

The information on drugs to be used in the clinical study including precautions for use is in Appendix 3, 4, and 5. The safety of all the study drugs to be used, with ingredients approved and marketed worldwide, is sufficiently guaranteed.

9.3 Concomitant medications

For any drug that will be concomitantly used from the consent obtainment through the end of the treatment

with the investigational product (Week 5; 37 ± 1 days) and may affect the endpoints, including hypertension, hyperlipidemia, diabetes and antiplatelet drugs, its prescription name, drug name, treatment duration, dosage and administration should be recorded.

9.4 Prohibited Concomitant Medications or Medications Requiring Caution

Drugs which can increase or decrease the effect of the investigational products such as CYP3A4 and P-gp inducers/inhibitors should be avoided. If concomitant use of these drugs is known, it should be immediately reported to the principal investigator. More information is described in Appendix 3, 4, and 5.

10 Safety Assessment

For adverse drug reactions reported in previous studies and unexpected adverse drug reactions that have not been verified in previous studies, the occurrence/non-occurrence and severity of each case will be checked, assessed and reported to the IRB and Seoul Asan Medical Center in accordance with the applicable regulations.

10.1 Definition of Adverse Event

An adverse event is defined as any untoward or undesirable sign (e.g., abnormalities in clinical laboratory test), symptom or disease occurring in a subject who are given the investigational product, and it does not necessarily have to have a causal relationship with the investigational product used in the clinical study. Any sign, symptom or disease occurring before subjects using the investigational product will not be considered as an adverse event.

10.2 Adverse Event Reporting Period

The period of adverse event collection in this study is from randomization to the post-study visit.

10.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) means the following adverse events or adverse drug reactions occurring at any dose of the investigational product:

- fatal or life-threatening;
- requiring inpatient hospitalization or prolongation of existing hospitalization;
- resulting in persistent or significant disability/incapacity;
- constituting a congenital anomaly/birth defect; or
- including other important medical events.

* However, pre-planned hospitalization does not constitute a serious adverse event.

10.4 Adverse Event Reporting Procedure

The principal investigator and subinvestigator should report all serious adverse events occurring during the study period to the applicable study center's IRB in accordance with the applicable local regulations regardless of causal relationship with the investigational product. The serious adverse event report form signed or provided by e-mail should be completed and reported to Asan Medical Center, the CRO, in one business day of knowledge. Any new information on serious adverse events until they are resolved should be reported to the center's IRB and CRO.

10.5 Assessment of Adverse Event Severity

Severity Assessment	Severity of adverse events will be classified according to the

	following criteria based on maximal intensity. 1) Mild: adverse event which does not interfere with the subject's normal activities of daily living, causes minimum inconvenience, and is easily bearable 2) Moderate: adverse event which causes considerable inconvenience to significantly interfere with the subject's normal activities of daily living 3) Severe: adverse event which makes the subject's normal activities of daily living impossible

10.6 Assessment of Causal Relationship

Assessment of causal relationship with the investigational product

Causal relationship with the investigational product will be classified into 6 levels as follows and the principal investigator or subinvestigator's opinion will be added.
The causal relationship with the investigational product will be classified into one of the following six categories and the principal investigator's or investigator's opinion will be added.

Causal Relationship	Rationale
Certain	• There is reasonable temporal relationship between drug administration and onset of an AE • The AE cannot be explained by other drugs, chemicals or concurrent diseases • The AE shows clinically reasonable response when the subject stops the drug • The AE is medically and phenomenally confirmed by rechallenge of the drug (only if feasible)
Probable /Likely (Probable /Likely)	• There is reasonable temporal relationship between drug administration and onset of an AE • The AE does not appear to be related to other drugs, chemicals or concurrent disease • The AE shows clinically reasonable response when the subject stops the drug • Information on rechallenge is not available.
Possible	• There is reasonable temporal relationship between drug administration and onset of an AE • The AE can be also explained by other drugs, chemicals or concurrent diseases. • Information on stopping the drug is not sufficient or available.
Unlikely	• The AE is a transient response which is unlikely to be related to drug administration • The AE can be also reasonably explained by other drugs, chemicals or potential underlying disease
None	• The AE occurs when the patient is not taking the drug. • The AE occurring before the patient takes the drug is not worsened after use of the device
Unassessable/ Unclassifiable	• Because information is insufficient or contraindicated, the information cannot be verified; and no further information is available or confirmed.

Robustness of relationship between the AE and investigational product (or

	other causes, progression of the underlying disease, and concomitant treatment) will be determined according to how well the AE can be explained from the perspective below: -- known pharmacological action of the investigational product - previous effect similar to the one observed in the investigational products or similar drugs - responses often reported to be related to similar drugs (e.g. vascular disease) - response related to duration of treatment with the drug (disappearing during the interruption of the treatment and recurring after rechallenge)

11 Statistical Analysis

11.1 Sample Size

Treatment group	Sample size
Warfarin group	98
Rivaroxaban group	98

11.2 Rationale for Sample Size

This is an exploratory study to assess the effects of rivaroxaban versus warfarin on ischemia, bleeding and hospital stay in acute cerebral infarction patients with nonvalvular atrial fibrillation. With a new design to compare the effects of warfarin and rivaroxaban in acute cerebral infarction patients, the study basically compares the incidence of 1) intracranial bleeding and 2) ischemic legions observed on the brain imaging.

Direct quotation is difficult due to few studies of acute cerebral infarction patients, but a study to compare the effects of rivaroxaban versus warfarin on the incidence of ischemia and bleeding in cerebral infarction patients showed the incidence of clinically significant intracranial bleeding was significantly lower in the rivaroxaban group than in the warfarin group (0.5 cases per year vs. 0.7 cases per year) (hazard ratio 0.67, 95% CI; 0.47-0.93). Previous studies from which the incidence of cerebral infarction or cerebral bleeding caused by aspirin plus warfarin in acute cardiogenic embolism include the International Stroke Trial[16]. This study revealed the incidence of recurrent cerebral infarction and cerebral bleeding within 14 days in the aspirin alone group is 4.9% and 0.4%, respectively. It also reported the incidence of recurrent lesions, intracranial bleeding or death was 20.7%. Based on those results, it is assumed that the incidence of recurrent cerebral infarction or brain bleeding is 5% and the incidence of ischemic brain lesions or bleeding lesions observed on MRI is 25-30%.

This study is not for confirmatory validation of the effects of the two drugs but for exploratory verification to see whether the effects of rivaroxaban is equivalent to those of warfarin. This study will consider the minimum difference in the effect that will allow further study, and will develop a hypothesis to continue further study only if rivaroxaban can reduce the incidence of ischemic or haemorrhagic brain lesions observed on MRI at least by 15-20% compared to warfarin.

Direct quotation of previous study results is difficult, but it is assumed that the incidence of intracranial bleeding or recurrent ischemic lesions confirmed by brain imaging is 25~30%. Based on the assumption, the sample size required to be able to verify the difference in the effect between warfarin and rivaroxaban is 15~20% is as follows:

Null hypothesis	The effect of rivaroxaban on the reduced incidence of intracranial bleeding and ischemic lesions is similar to that of warfarin.
Alternative hypothesis	Rivaroxaban will reduce the incidence of intracranial bleeding and ischemic lesions at least by 15~20% compared to warfarin.

In order to calculate the expected sample size with the 5% (one-sided) significance level and 80% power:

1) 89 subjects are required per group for hypothesis testing if it is assumed the incidence of intracranial bleeding or recurrent ischemic lesions is 25% and the least significant difference (LSD) is 15%;

2) 56 subjects are required for hypothesis testing if it is assumed the incidence of intracranial bleeding or

recurrent ischemic lesions is 30% and the LSD is 20%.

Considering dropout and inaccurate expected incidence of events due to a lack of previous studies, it is planned to recruit 98 subjects per group.

11.3 General Principles of Statistical Analysis Method

For all the variables used for this study, the frequency and proportion of categorical data will be presented, and the summary statistics of continuous data will be provided using the mean and standard deviation. The basic method for all statistical tests to be used for analyses will be two-sided tests except for the primary endpoints (the recurrent incidence of intracranial bleeding and ischemic lesions). The statistical significance will be tested at a 5% significance level, and, if necessary, a two-sided 95% confidence interval will be provided.

If the variables are verified that show the difference between the groups after randomization including age and baseline test results except for efficacy and safety analyses, a regression model will be introduced which can adjust and analyse the risk or prognostic factors for endpoints.

- Analysis set

  The analysis sets required to assess the efficacy and safety in this study will be compliant with the local and international standards. The efficacy analysis will include both the ITT and PP analysis sets as defined below; the safety analysis will be defined and carried out as below:

- Efficacy analysis set:

  1) Modified intention to treat (modified ITT)

  The modified ITT is defined as all subjects randomized after giving the consent to participation in the study. However, the subjects who have never taken the investigational products (warfarin and rivaroxaban) or had no efficacy endpoints measured in the ITT set even after taking the investigational products will be excluded from the analysis.

  2) Per protocol (PP)

  The subjects in the modified ITT, who do not violate the inclusion/exclusion criteria and have rivaroxaban or warfarin compliance of≥80% will be included in the analysis.

  The efficacy analysis will be performed for both ITT and PP analysis sets and the analysis results will be presented in the clinical study report.

- Safety analysis set:

  The safety analysis set is defined as all the subjects who are randomized after giving consent to participation in the study and have taken the investigational product (warfarin or rivaroxaban) at least once.

- Handling of Missing value

  If there is any missing value regarding the efficacy endpoints including the primary endpoint, the missing value will be excluded and the analysis will be carried out. For variables other than the primary efficacy endpoint, missing values will be handled using LOCF (last observed carried forward); for the safety endpoints, LOCF will not be used.

11.4 Efficacy and Safety Endpoint Analysis Methods

1) Efficacy endpoints

- Primary efficacy endpoint

  The primary endpoint of this study is defined as the incidence of 1) intracranial bleeding or 2) recurrent ischemic lesions based on brain imaging taken at Week 4. For inter-group comparison, the difference will be tested as described above: the LSD of 15% will be established if the incidence of bleeding and ischemic lesions is about 25%, and the LSD of 20% will be established if the incidence is about 30%.

- Secondary efficacy endpoints

The secondary endpoints will be compared by the following methods:

1) inter-group comparison of the incidence of intracranial bleeding confirmed by brain imaging at Week 4 and 2) for inter-group comparison of the incidence of recurrent ischemic lesions confirmed by brain imaging at Week 4, chi-square test or Fisher's exact test will be used.

3) Total number of days of hospital stay after randomization: t-test and log-rank test

4) For inter-group comparison of the incidence of major bleeding and acute artery syndrome (myocardial infarction or unstable angina), chi-square test or Fisher's exact test will be used.

5) Incidence of major vascular events: For stroke, myocardial infarction or vascular death, the incidence will be tested by chi-square test of Fisher's exact test. If the time of the event is measured, the incidence is assumed by the Kaplan-Meier method and compared by the log-rank test.

4) The incidence of 4) major vascular events and major bleeding and 5) clinical ischemic events will be compared between the groups by chi-square test or Fisher's exact test.

6) mRS scores at Week 4 (30 ± 5 days) will be compared by chi-square test or nonparametric method.

2) Safety endpoints

The safety analysis will be carried out based on all adverse events, clinical laboratory results, NHISS, 12-lead ECG and vital signs (SBP/DBP and pulse) collected from the subjects.

All safety variable data above collected during baseline, randomization and treatment will be provided by time point when the safety endpoints are measured and by patient, and the summary statistics will be presented. The adverse events observed after use of the investigational product will be summarized. The number of patients who have experienced adverse events, adverse drug reactions, serious adverse events, death, adverse events causing study discontinuation, and/or "other significant adverse events (OAEs) will be summarized by group. The number of subjects who developed each adverse event will be summarized by group using the recommended terms (e.g. MedDRA) by SOC and by maximum severity. Apart from summary statistics, the intergroup incidence and number of adverse events will be assessed using the chi-square test, Fisher's exact test or Poisson regression analysis. The incidence of abnormal laboratory results, NIHSS, and 12-lead ECG will be analyzed using the chi-square test, Fisher's exact test or Poisson regression analysis to compare the incidence of abnormalities between the groups at each time point. For vital signs, summary statistics of continuous data will be presented at each time point, and intergroup comparison will be carried out using the generalized linear model (GLM) or generalized linear mixed model (GLMM).

12 Measurement of Investigational Product Compliance

Based on the drug purchase receipts for the treatment group, the number of days when the drugs should be taken will be documented. At Day 5 and Week 4 OPD visit, the number of days when the drugs were actually taken will be stated based on the number of the returned drugs to verify drug compliance. Compliance will be calculated based on the medication history of warfarin and rivaroxaban.

$$\text{Adherence (\%)} = \frac{\text{No. of days when drugs were actually taken}}{\text{No. of days when drugs should be taken}} \times 100$$

13 Premature Termination and Withdrawal Criteria

The principal investigator may terminate the study participation of the subject or withdraw him/her from the study in any of the followings:

- ✓ the principal investigator judges that the study participation of the subject should be terminated due to an adverse event;

- ✓ the principal investigator judges that the study participation of the subject should be terminated due to exacerbation of the symptom;
- ✓ the subject is proven ineligible for the study after the beginning of the study; or
- ✓ the principal investigator considers it inappropriate to continue the study.
- ✓ the subject becomes pregnant during participation in the study

Treatment after study treatment completion/termination/withdrawal should be carried out according to the investigator's discretion. In case of study end/termination/withdrawal due to onset of an adverse event or for a safety reason, the adverse event should be followed up until it is resolved if possible, and the relative matters should be recorded in the CRF.

14 Efficacy Analysis

1. Imaging results should be collected from the centralised server so that they can be analysed and interpreted by the IIRC. Data supplementation can be requested during the analysis and interpretation; if so, the center should reply and/or deliver supplementation data as soon as possible.
2. The hospital stay should be recorded in a unit of day based on each center’s medical records.

15 Measures To Ensure Subject Safety

The study center must take all possible measures to ensure subject safety, being equipped with all equipment and professionals required for the clinical study to be properly conducted according to all the applicable regulations as specified in the protocol. The subinvestigators must be fully aware of adverse events and precautions prescribed in the protocol before the study initiation. If a serious adverse event occurs during the study, they must immediately discontinue the study participation of the subject in question, take an appropriate measure and inform IRB of the event.

16 Subject Informed Consent Form, Compensation and Subject Care and Treatment after End of Study

16.1 Subject Information and Informed Consent Form

The investigator should provide sufficient information on the clinical study and efficacy and safety of the investigational product for the potential subject, obtain the consent form dated and signed by the subject (if necessary, his/her representative) under the subject's voluntary consent, and provide one copy each of the informed consent form and subject information sheet before the subject's participation in the study. If the subject or his/her representative cannot read, an impartial witness is required. Also, the subject information sheet and consent form to be provided for the subject should be used only after approved by each study center's IRB.

16.2 Agreement on Compensation

If any adverse event induced by the clinical study causes an injury to the subject, the sponsor will provide compensation according to the agreement on subject compensation.

16.3 Subject Care and Treatment After Completion of the Study

The care and treatment of the subject who has completed the study will comply with the routine medical care and treatment practices. After the end of this study, further treatment will be determined based on the subject' clinical condition and the study doctor's discretion.

17 Considerations for safe and scientific conduct of the study

17.1 Compliance with Protocol and Protocol Amendment

This study will be conducted according to the protocol approved by the IRB and MFDS. All amendments to the protocol will be determined through discussion between the sponsor and the principal investigator. The investigator should obtain the prior approval for any amendment to the protocol except for immediate prevention of harm to the subject. However, if the protocol is amended and used before the approval from the regulatory authorities for immediate prevention of harm to the subject, this amendment should be reported to the regulatory authorities as soon as possible.

If the protocol cannot be complied with during the study for an unavoidable reason along with violation for the sake of subject safety, the investigator should record the violation in the source documents and CRF, inform it to the CRO and monitor, and appropriately report it to the regulatory authorities according to each study center's regulations. The CRO, after receiving report on violation, will decide whether or not to continue the study for the concerned subject and inform the investigator.

17.2 Study Monitoring

This study is an investigator-initiated trial, and the CRO will provide appropriate study conduct guidelines for each participating center and designate the monitor who will monitor the study and carry out monitoring through visits to study centers before and during the study or web-based CRFs. The monitoring schedule will be determined through discussion with the person in charge from the applicable center, and whether the study is being conducted appropriately according to the protocol and applicable regulations will be checked at monitoring visit. Any finding at monitoring, if necessary, should be appropriately resolved through discussion with the investigator.

17.3 Retention of Clinical Study-related Documents and Data

The principal investigator is responsible for maintaining and providing essential study documents. An essential study document means a document that enables individual or full assessment of study conduct and quality of the resulting data. Essential study documents include all source documents, monitoring records and appointment schedule, correspondences exchanged between the sponsor and investigator, and documents set forth by the GCP. Source documents include all observation records, clinical study activity records, and all reports and records required for assessment and reconstruction. Therefore, the records on all the treatments and procedures performed based on the protocol and all similar records are also included in source documents. The study center should retain the documents related to the study for three years from the study end date.

17.4 Confidentiality of Clinical Study Data and Subject Records

All the subjects' names should be kept confidential, and the subjects should be managed and evaluated using the code number and initials given at the beginning of the study. All the records on the subjects' identities should be managed in the way to keep them confidential. However, the monitor, auditor, IRB, and a person designated by the MFDS can have access to the records on the subjects to validate reliability of the study procedures and data to the extent provided by the applicable regulations which does not breach subject confidentiality.

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STATISTICAL ANALYSIS PLAN

Rivaroxaban versus Warfarin in acute ischemic stroke with atrial fibrillation: Acute stroke with Xarelto to reduce intracranial bleeding, recurrent embolic stroke, and hospital stay, phase 2, conceptual multicenter trial

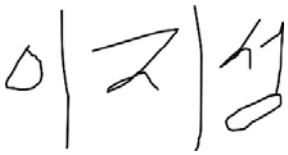
Triple-AXEL Study
Clinical Trial No. LMI-2013-1013

Author: Ji Sung Lee, Ph.D., Clinical Research Center, Asan Medical Center
Version: 1.0
Issue/Report Date: 2016.02.25

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

SIGNATURE PAGE

Prepared by :



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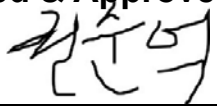

Sun U. Kwon, MD, Ph.D. / Principal Investigator Department of Neurology, Asan Medical Center	2016/02/25 Date (yyyy/mm/dd)

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ABBREVIATION

ABBREVIATION	DEFINITION
AE	Adverse Event
CRF	Case Report Forms
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DWI	Diffusion Weighted Image
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ITT	Intention to Treat
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PP	Per Protocol
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure

1. INTRODUCTION

1.1. Purpose of Statistical Analysis Plan

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Triple-AXEL study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), or future manuscripts. Also post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP

- Protocol for Triple-AXEL study Version 3.2 Final issued 10th May 2015
- CRF for Triple-AXEL study
- ICH Guidance on Statistical Principle for Clinical Trials (E9).

2. STUDY OBJECTIVE

To assess the effects of warfarin or rivaroxaban after four-week treatment (30 ± 5 days) in acute cerebral infarction or transient ischemic attack with nonvalvular atrial fibrillation based on the independent investigator's brain image interpretation.

3. STUDY DESIGN

3.1. Overview

This is a phase 2, multicenter (12 institutions in South Korea), randomized, open label, blinded endpoint evaluation (PROBE) trial to compare the safety and efficacy of rivaroxaban vs. warfarin in patients with acute ischemic stroke or TIA due to presumed AF-related cardioembolism.

3.2. Sample Size

The primary endpoint for the study is the composite of intracranial bleeding and recurrent ischemic lesion on MRI at four-weeks after randomization. The sample size is based on the data gained from earlier studies [1, 2, 3]

We calculated the sample size by assuming that the primary endpoint rate would be 25% in the warfarin group and that the absolute risk reduction with rivaroxaban would be 15%. With 80% power and a one-sided level of significance of 0.05, 89 patients are required per treatment group. Assuming a 10% dropout rate, 196 patients will be recruited.

The software PASS version 12 (NCSS, LLC. Kaysville, Utah, USA) was used for the sample size calculation.

3.3. Randomization

After screening, eligible patients will be randomly allocated to rivaroxaban or dose-adjusted warfarin (target INR 2–3) in a 1:1 ratio using an interactive web response system. Allocation will be by randomly permuted blocks and stratified by centre to enhance balance.

3.4. Populations

3.4.1. Target population

The target population is patients with acute cerebral infarction or transient ischemic attack associated with non-valvular atrial fibrillation that meet all the inclusion and exclusion criteria and who are considered eligible to be entered into this clinical investigation.

3.4.2. Modified Intention-to-treat (modified ITT)

The modified ITT is defined as all subjects randomized after giving the consent to participation in the study. However, the subjects who have never taken the investigational products (warfarin and rivaroxaban) or had no efficacy endpoints measured in the ITT set even after taking the investigational products will be excluded from the analysis.

3.4.3. Per Protocol (PP)

The subjects in the modified ITT, who do not violate the inclusion/exclusion criteria and have rivaroxaban or warfarin compliance of≥80% will be included in the analysis.

3.4.4. Safety Population

The safety population is defined as any patient who received at least one administration of either treatment.

4. EFFICACYS AND SAFETY ENDPOINTS

4.1. Primary Endpoint

- The composite of intracranial bleeding and recurrent ischemic lesion on MRI at four-weeks after randomization

4.2. Secondary Endpoints

- Intracranial bleeding confirmed by brain imaging after 4 weeks treatment
- Recurrent ischemic lesion confirmed by brain imaging after 4 weeks treatment
- The total number of days of neurology division stay after randomization
- Major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) definition
- Acute artery syndrome (myocardial infarction or unstable angina)
- Major vascular events: stroke, myocardial infarction, or vascular death (including bleeding and ischemic vascular events)
- Major vascular events and major bleeding (defined by the ISTH)
- Clinical ischemic events: recurrent cerebral infarction, myocardial infarction, other ischemic events requiring vascular intervention and ischemic vascular death
- The mRS (modified Rankin scale) 0-1 after 4 weeks treatment (30 ± 5 days)

4.3. Safety Endpoints

- Incidence of all of adverse events and serious adverse events

5. GENERAL CONSIDERATIONS OF STATISTICAL ANALYSIS

5.1. General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary endpoints. In general, summaries will be presented by patient population and by treatment groups and/or overall.

In general, continuous variable summaries will include the number of patients (N) (with non-missing values), mean, standard deviation (SD), median, interquartile range (1st and 3rd quartile), minimum and maximum.

Categorical variable summaries will include the frequency and percentage of patients who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of patients in the study population for the treatment groups and/or overall, unless otherwise specified.

The hypothesis testing for primary endpoint will be carried out at the one-sided 5% level of significance. In all secondary and safety endpoint, a two-sided 5% level of significance will be used. All secondary endpoints are exploratory and therefore no adjustment for multiple testing will be applied.

5.2. Handling of Missing Data

No adjustment for missing data will be applied. For all analyses missing data will be excluded from the analyses.

5.3. Rounding

All results will be presented to two decimal places or an appropriate number of significant figures for the magnitude of the results.

5.4. Statistical Software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS® version 9.4 [4].

6. STATISTICAL METHODS

6.1. Primary endpoint

The primary endpoint for the study is the composite of intracranial bleeding and recurrent ischemic lesion on MRI at four-weeks after randomization. Analysis will be carried out using Chi-square test or Fisher's exact test. The estimated relative risk and absolute risk difference between two groups will be presented along with their 95% confidence intervals.

This analysis will be carried out on a number of different populations to ensure robustness in the results:

- modified ITT Population
- PP Population

6.2. Secondary endpoint

The following endpoints will be analyzed using Chi-square test or Fisher's exact test to investigate the treatment effects:

- Intracranial bleeding confirmed by brain imaging after 4 weeks treatment
- Recurrent ischemic lesion confirmed by brain imaging after 4 weeks treatment
- Major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) definition
- Acute artery syndrome (myocardial infarction or unstable angina)
- Major vascular events: stroke, myocardial infarction, or vascular death (including bleeding and ischemic vascular events)
- Major vascular events and major bleeding (defined by the ISTH)
- Clinical ischemic events: recurrent cerebral infarction, myocardial infarction, other ischemic events requiring vascular intervention and ischemic vascular death
- The mRS (modified Rankin scale) 0-1 after 4 weeks treatment (30 ± 5 days)

For the following continuous endpoints the Wilcoxon rank sum test or Student's t-test will be used as appropriate. In order to test if the underlying assumptions of normality required for Student's t-test are valid the Shapiro-Wilk test will be performed. If the Shapiro-Wilk test indicates that there are significant violations of underlying normality (p-value < 0.05) the Wilcoxon rank sum test will be used.

- The total number of days of neurology division stay after randomization

All secondary endpoint analyses will be carried out on a number of different populations to ensure robustness in the results:

- modified ITT Population
- PP Population

6.3. Multivariable Analysis

If there is a significant difference between the groups at baseline, multivariable analysis for primary and secondary endpoint will be conducted to adjust baseline imbalances. Multivariable analysis will be carried out using an analysis of covariance (ANCOVA) and Poisson regression according to the type of endpoints. Confounders to include in multivariable analysis are the stratification variable (site), clinical relevant variables and statistically significant baseline characteristics ($p<0.1$).

6.4. Safety analysis

The analysis of safety assessment in this study will include summaries of the following categories of safety data collected for each patient and will be presented for the Safety Population.

6.4.1. Adverse Event

The primary safety parameter is the occurrence of adverse event (AE) and serious adverse event (SAE). All data will be summarized within each treatment group. All SAEs and AEs will be listed using coding for System Organ Class and Preferred Term (using the MedDRA version 17.0).

An AE summary table will be presented including row with the number of patients with

- Adverse Event (AE)
- Adverse Drug Reaction (ADR)
- Serious Adverse Event (SAE).
- AE leading to discontinuation of study drug
- AE leading to death

AE will be summarized as follows:

- Number and percentage of patients with AEs classified by System Organ Class and Preferred Term
- Number and percentage of patients by severity, System Organ Class and Preferred Term
- Number and percentage of patients by relationship to randomized study medication, System Organ Class and Preferred Term
- Number and percentage of patients with SAEs classified by System Organ Class and Preferred Term

A data listing of SAEs will be provided.

6.4.2. Concomitant Medication

Incidence of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 1 and ATC level 2 by treatment group.

6.5. Additional summaries

All demographic and baseline characteristics will be summarized by treatment group and across the whole trial. For continuous variables, descriptive statistics will be presented (mean, standard deviation, median, minimum, maximum, interquartile range and number of participants with data). For categorical variables, percentages and number of participants with data will be presented. The denominator for the percentages will be the number of patients with non-missing data.

Summaries will include the following:

- Patient disposition and reasons for withdrawal
- Patient demography (e.g. age, sex, etc.)
- Baseline vital sign (SBP, DBP, Pulse)
- Baseline laboratory test
- Baseline stroke characteristics (e.g. mRS, NIHSS, HAS BLED Score, CHA2DS2-VASC Score, Initial DWI volume, etc.)
- Treatment exposure: Compliance to study drug

6.6. Interim Analysis

We will perform a total of two formal analyzes (one interim analysis and one final analysis) in this study. When a majority of subjects (100) have completed the study, the interim safety analysis will be carried out in order to determine whether or not to continue the study. The safety analysis will be done by an independent statistician and no adjustment for multiple testing will be applied.

7. REFERENCE

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