CLINICAL STUDY PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY OF DU-176B IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION AGED 80 YEARS OR OLDER WHO ARE INELIGIBLE FOR AVAILABLE ORAL ANTICOAGULATION THERAPY

Sponsor: Daiichi Sankyo

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PROTOCOL SYNOPSIS

Protocol Number:	DU176b-C-J316
Investigational Product:	DU-176b
Generic Name:	edoxaban tosylate hydrate
Study Title:	A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of DU-176b in patients with nonvalvular atrial fibrillation aged 80 years or older who are ineligible for available oral anticoagulation therapy
Phase of Development:	Phase 3
Planned Indication:	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)
Study Objective:	To evaluate the efficacy and safety of 15 mg of DU-176b in patients with NVAF aged 80 years or older who are ineligible for available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the approved dosage.* To evaluate the superiority of 15 mg of DU-176b compared to placebo in a composite endpoint of stroke and systemic embolism as the primary efficacy endpoint.
Study Design:	A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven study
Planned Study Duration:	24 May 2016 to 30 Sep 2020
Study Sites:	See Attachment 1
Planned Sample Size:	A total of 800 subjects (400 in the DU-176b group and 400 in the placebo group)
Subject Eligibility Criteria:	Inclusion Criteria • History of atrial fibrillation (AF) documented by any electrical tracing within the 1 year prior to the day of informed consent • $CHADS_2$ index score ≥ 2 • Patients with age ≥ 80 years on the day of informed consent • Patients who are ineligible for available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at

*: For warfarin, international normalized ratio (INR) controlled at between 1.6 and 2.6

the approved dosage, and with at least 1 of the following bleeding risks:

i) Severe renal impairment (creatinine clearance [CLcr] calculated by the Cockcroft-Gault formula ≥ 15 mL/min and < 30 mL/min)
ii) History of bleeding from critical area or organ (such as intracranial, intraocular, or gastrointestinal bleeding)
iii) Low body weight (≤ 45 kg)
iv) Continuous use of acidic non-steroidal anti-inflammatory drugs (NSAIDs)
v) Patients using 1 antiplatelet drug (for a purpose other than prophylaxis of cardioembolic stroke)

Major Exclusion Criteria

- Transient AF secondary to other reversible disorders
- Patients who received dabigatran, rivaroxaban, apixaban, or edoxaban within the 8 weeks prior to the day of randomization
- Patients receiving warfarin with INR controlled at ≥ 1.6 in 2 of the 3 most recent examinations, including the eligibility assessment examination, measured at least 4 weeks apart (subjects with INR ≥ 1.6 at the eligibility assessment examination are excluded)
- Patients with particularly high bleeding risk meeting any of the following criteria:
  i) Active bleeding on the day of informed consent
  ii) Unresolved peptic ulcer on the day of informed consent
  iii) Hemoglobin < 9 g/dL, or platelet count < $10 \times 10^4/\mu L$ at the eligibility assessment examination
  iv) Hereditary hemorrhagic disease
- Cerebral infarction or transient ischemic attack within the 30 days prior to the day of randomization
- Uncontrolled hypertension (systolic blood pressure persistently > 160 mmHg or diastolic blood pressure persistently > 100 mmHg)
- CLcr calculated by the Cockcroft-Gault formula < 15 mL/min

	• Patients who have started hemodialysis or who may start hemodialysis by the time of the examination at completion of study treatment • Patients receiving dual antiplatelet therapy at the time of informed consent, or those expected to receive dual antiplatelet therapy after the time of informed consent, who cannot safely discontinue use of either of the antiplatelet drugs • Patients with hepatic function disorder accompanied by coagulation disorder • History of acute myocardial infarction within the 30 days prior to the day of randomization • Serious heart disease such as cardiac failure with New York Heart Association (NYHA) classification ≥ 3 or unstable angina pectoris
Dose and Route of Administration:	DU-176b 15 mg or placebo will be administered orally once daily. Administration of the study drug will be continued until the examination at completion of study treatment performed within 60 days after the declaration of completion of the study. Completion of the study will be declared when the planned number of subjects with primary efficacy endpoint events has been collected. The planned mean duration of study treatment is 2 to 2.5 years. When the investigator or subinvestigator requires to know the study treatment assignment for each subject to determine the subsequent treatment after the final administration of the study drug, the study treatment can be continued until the final follow-up examination after obtaining consent from the subject. The planned duration of the additional study treatment from the examination at completion of study treatment to the final follow-up examination is 3 to 4 months.
Prohibited Concomitant Medication:	• Anticoagulants • Thrombolytic drugs • Antiplatelet drugs (including over-the-counter drugs containing aspirin) administered to reduce the risk of cardioembolic stroke based on AF, dual antiplatelet therapy
Study Procedures:	See the study procedure and specimen collection schedule (page 5)

Endpoints:	Primary Endpoints Efficacy: Composite of stroke and SEE Safety: Major bleeding Secondary Endpoints Efficacy: • Composite of stroke, SEE, and death due to CV • Major adverse cardiovascular events (MACE)† • Stroke, systemic embolism, and all-cause mortality • Stroke, systemic embolism, major bleeding, and all-cause mortality • All-cause mortality Safety: • Major bleeding and clinically relevant non-major bleeding • Clinically relevant non-major bleeding • Minor bleeding • All bleeding events
Primary Statistical Analysis:	For the composite endpoint of stroke and systemic embolism observed from randomization up to the examination at completion of study treatment, the time to onset of the initial event, the treatment group will be compared based on a Cox proportional hazard model with the $CHADS_2$ score (≤ 2 or ≥ 3) as covariate. (significance level: 5%, 2-sided)

†: Non-fatal myocardial infarction, non-fatal stroke, non-fatal systemic embolism, or deaths due to cardiovascular disease or bleeding

Table of Study Procedure and Specimen Collection Schedule

	Eligibility assessment examination		Duration of study treatment: Every 4 weeks from Week 4 to Week 48	Duration of study treatment: Every 8 weeks from Week 48 onward	Examination at completion of study treatment[a]/examination at discontinuation	Final follow-up examination[b]
Visit	0	1	2–13	14–		
Visit window	Within the 30 days prior to randomization[c]		± 14 days[c]	± 14 days[c]	Within the 60 days after declaration of completion of the study[c] Within the 7 days after discontination[c]	Within the 30 to 37 days after examination at completion of study treatment[c]
Informed consent	X					
IRT entry (entry of subject information)	X					
Baseline subject characteristics[d]	← X →					
IRT entry (entry of eligibility assessment result), randomization		X				
Study drug administration		←	←	←	→ [e]	← - - - → [f]
Study drug compliance		←	←	←	→	
Height	← X →					
Physical examination/medical interview	← X→		X	X	X	X
Body weight	← X→		X	X	X	X
Blood pressure/pulse rate	← X→		X	X	X	X
Hematology test[g]	← X→		X[h]	X	X	X
Blood chemistry test[g]	← X→		X[h]	X	X	X
Endocrinology test[g]	← X→		X[h]	X	X	X
Urinalysis[g]	← X→		X[h]	X	X	X
CLcr[i]	← X→		X[h]	X	X	X
12-lead ECG	← X→		X[j]	X[k]	X	X
Head CT or MRI[l]	← X→					
Whether surgery or hospitalization occurred		←	←	←	→	
Adverse events		←	←	←	→	→ [m]
Efficacy/bleeding events		←	←	←	→	
Concomitant medication	←	←	←	←	→	
Follow-up survey after interruption/discontinuation of study drug[n]			←	←	→	
Pharmacokinetic blood sampling[g]			X[o]			
Blood sampling for pharmacodynamic indicators[g]		X				
Blood sampling for biomarker measurement[g]		X	X[o]			
PGx banking[p]	← X[q] →					

a: Will not be performed on subjects withdrawn from the study.
b: Will be performed in subjects who continue the study treatment, in principle, within a month after notifying their study treatment assignments.
c: Will be calculated by taking the date of the scheduled visit to be Day 0.
d: Falling score, frailty assessment, and one-leg standing test with eyes open will be surveyed by the

time of Visit 3.

e: Study treatment will be started on the same date that notification of study drug identifiers is given. Study treatment will be continued until the examination at completion of study treatment, which will be performed within the 60 days after the declaration of completion of the study that is made when the planned number of subjects with primary efficacy endpoint events (stroke and systemic embolism) has been collected.

f: The study drug will be administered only to subjects who provided consent for the additional study treatment during the period from the examination at completion of study treatment to the final follow-up examination.

g: These will be measured at the central laboratory.

h: Will be performed once every 8 weeks (Week 4 to Week 48: Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, Visit 13/Week 48 onward: Visit 14, Visit 15, Visit 16...).

i: Will be calculated with the Cockcroft-Gault formula.

j: Will be performed once every 12 weeks (Visit 4, Visit 7, Visit 10, Visit 13).

k: Will be performed once every 24 weeks (Visit 16, Visit 19, Visit 22...).

l: If this is performed within 4 weeks before the day of informed consent as part of a physical examination, the results may be used for the eligibility assessment examination, with the consent of the subject.

m: During the period from the examination at completion of study treatment to the final follow-up examination, only serious adverse events will be monitored.

n: Checks on whether serious adverse events have occurred, whether efficacy events have occurred, whether bleeding events have occurred, whether the following drugs have been used: anticoagulants, thrombolytics, antiplatelet drugs, intravenous antiarrhythmics, and acidic NSAIDs, blood pressure/pulse rate (if the subject has made a visit), and laboratory tests determined to be appropriate by the investigator or subinvestigator (if the subject has made a visit. If warfarin is being used, measurement of PT-INR is mandatory) will be conducted every 8 weeks.

o: Will be performed on Visit 3.

p: Will be performed only at study sites where it is possible.

q: Will be performed from Visit 2 onwards.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

Abbreviation	Definition
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	L-alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	L-aspartate aminotransferase
BMI	body mass index
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CK	creatine kinase
CLcr	creatinine clearance
CT	computed tomography
CV	cardiovascular
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
F1+2	prothrombin fragment 1+2
GCP	good clinical practice
GGT	gamma glutamyl transferase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-treat
IWRS	interactive web response system
LC-MS/MS	liquid chromatography tandem mass spectrometry
LDH	lactic acid (lactate) dehydrogenase
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	Modified intent-to-treat
MRI	magnetic resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics

PK	pharmacokinetics
PPS	per protocol set
PT	prothrombin time
PTE	pulmonary thromboembolism
PT-INR	prothrombin time expressed as international normalized ratio
SEE	systemic embolic event
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
VKA	vitamin K antagonist
VTE	venous thromboembolic event
Xa	activated coagulation factor X

1. INTRODUCTION

Atrial fibrillation (AF) is a common type of arrhythmia in the elderly, and is an independent risk factor for stroke.[1),2)] Since aging is also an independent risk factor for stroke, and since in general many elderly people also have concurrent risk factors such as hypertension or congestive cardiac failure, elderly patients with AF are a population at high risk from stroke.[3),4)] It is known that the prevalence of AF increases with age,[5)] and given that the Japanese population is set to age further in the future, there is considered to be an increasing trend in the number of elderly patients with AF at high risk from stroke. Many strokes that occur in patients with AF are cardioembolic strokes, and as they are often severe, they are a factor that increases the burden of nursing care due to sequelae and long-term extension of hospitalization periods. For these reasons, and also to prevent patients from becoming bedridden, the prevention of stroke in elderly patients with AF is highly clinically significant.

Not only in Japan but also globally, oral anticoagulant therapy is recommended as the standard of care for the prevention of stroke in patients with AF.[6),7)] Assessment of whether oral anticoagulant therapy is indicated for a patient is made based on whether risk factors for stroke are present. If the $CHADS_2$ index score, an assessment indicator for the risk of stroke in patients with AF, is used, oral anticoagulant therapy is recommended or suitable for consideration in patients aged 75 years or older even if they do not have any other risk factors.[6)] As stated above, elderly patients with AF are a population with a particularly high risk of stroke, for which oral anticoagulant therapy to prevent stroke is recommended. However, in clinical practice, oral anticoagulant therapy is often not aggressively administered to elderly patients with AF. According to tabulated data as of Jun 2012 in The Fushimi AF Registry,[8)] a survey centering on Fushimi-ku in Kyoto City whose objectives include surveying the baseline factors of patients with AF, surveying the state of their treatment, and following up on their prognoses, oral anticoagulant therapy was not administered to at 50% or more of patients with AF in their 80s and 70% or more of patients with AF in their 90s. In addition, almost all patients in their 80s or older have a $CHADS_2$ index score of at least 2. Thus, the survey shows that there are many patients not receiving oral anticoagulant therapy despite having a high risk of stroke. In tabulated data as of Jul 2014 in The Fushimi AF Registry,[9)] oral anticoagulant therapy was not administered to 58.7% of patients with AF aged 85 years or older. Similar situations have also been reported overseas.[10),11),12)]

One major reason that oral anticoagulant therapy is not aggressively administered is that there is a high risk of bleeding in elderly patients with AF. Aging itself is a bleeding

risk for oral anticoagulant therapy, and in recent years, clinical studies of non-vitamin-K-antagonist oral anticoagulants conducted in patients with AF have also shown that the subgroup of elderly patients tends to have a higher incidence of bleeding events.[13),14),15),16),17)] Among elderly patients with AF, there are patients with further bleeding risks, such as a medical history of bleeding, a falling risk, renal impairment, and concomitant antiplatelet medication, and it is thought that administration of oral anticoagulant therapy is unsuitable for these patients. Thus, despite the high risk of stroke in elderly patients with AF, there are currently more than a few cases where the standard therapy, oral anticoagulant therapy, is not administered because of concerns about bleeding, and so it is considered that an oral anticoagulant therapy with a reduced bleeding risk is necessary in clinical practice.

DU-176b (generic name: edoxaban tosilate hydrate) is an oral anticoagulant that specifically and reversibly inhibits activated plasma clotting factor X, and is used in clinical practice as Lixiana® Tablets 15 mg, 30 mg, and 60 mg with the indication to reduce the risk of stroke and systemic embolic events (SEEs) in patients with nonvalvular atrial fibrillation (NVAF). In a phase 3 global study (ENGAGE AF-TIMI 48) in patients with NVAF, edoxaban 60 mg (or 30 mg in subjects with factors requiring dosage adjustment‡) administered orally once daily was found to be non-inferior to warfarin for composite of stroke and SEE, and thus the approved dosage in patients with NVAF is 30 mg or 60 mg orally once daily. In the ENGAGE AF-TIMI 48 study, the efficacy and safety of edoxaban administered orally at 30 mg (or 15 mg in subjects with factors requiring dosage adjustment) once daily (edoxaban 30-mg group) were evaluated. The edoxaban 30-mg group was also found to be non-inferior to warfarin for composite of stroke and SEE, but when analysis was restricted to oral administration of 15 mg once daily in the subjects with factors requiring dosage adjustment, the annual incidence of composite of stroke and SEE was higher than in the warfarin group, particularly in the Japanese population (2.79%/year vs. 1.20%/year, Cox proportional hazards model $P = 0.1141$). Thus, the ENGAGE AF-TIMI 48 study comparing edoxaban with warfarin, where the international normalized ratio (INR) was strictly controlled, did not clearly show the efficacy of edoxaban 15 mg administered orally once daily, and at present, 15 mg once daily is not recommended as a dosage in administration to patients with NVAF.

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‡ Factors requiring dosage adjustment were any of the following: body weight ≤ 60 kg, creatinine clearance (CLcr) ≤ 50 mL/min, or concomitant administration of verapamil or quinidine

However, the annual incidence of composite of stroke and SEE in the population administered edoxaban at 15 mg once daily due to dosage adjustment at the time of random assignment in the edoxaban 30-mg group of the ENGAGE AF-TIMI 48 study was 2.36%/year for the overall population and 2.79%/year for the Japanese population (2.21%/year and 1.20%/year respectively, in the warfarin group). In meta-analysis using data from randomized clinical studies of vitamin K antagonists (VKAs) conducted in patients with AF in the past, it was reported that the annual incidence of non-fatal stroke in the control group (untreated) was 7.6%/year (2.5%/year in the VKA group).[18] However, at present, due to changes in the medical environment, the incidence of the events stroke or SEE may have decreased, but it is still considered to be a high incidence. Given these results, it is expected that even if edoxaban is administered at 15 mg once daily, it will be effective at reducing the risk of stroke to a certain extent, based on its anticoagulant effect. The annual incidence of composite of stroke and SEE during administration of edoxaban at 15 mg once daily in subjects aged 80 years or older in the ENGAGE AF-TIMI 48 study was 2.33%/year for the overall study population, which is similar to the result (2.36%/year) for all subjects administered 15 mg once daily regardless of age. In addition, in the AVERROES study[16] evaluating the efficacy of apixaban in patients with AF and VKA is not indicated, the annual incidence of composite of stroke and SEE in the aspirin group, which was the control group, was 3.7%/year, and thus the annual incidence during administration of edoxaban at 15 mg once daily in the ENGAGE AF-TIMI 48 study was lower than this. Aspirin is not positioned as a standard of care for reducing the risk of stroke in patients with AF, and is not recommended as antithrombotic therapy in patients with AF,[6] but it is expected that administration of edoxaban at 15 mg once daily will show a greater reduction of the risk of stroke than aspirin.

From the safety standpoint, no hemorrhagic stroke was found during administration of edoxaban at 15 mg once daily in the ENGAGE AF-TIMI 48 study, and the annual incidence of intracranial hemorrhage was 0.14%/year, lower than the incidence in the warfarin group of 1.26%/year, and also lower than the incidence of 0.57%/year in subjects administered edoxaban at 30 mg once daily due to dosage adjustment. The annual incidence of major bleeding was 1.50%/year with administration of edoxaban at 15 mg once daily, which was lower than the incidences of 4.85%/year in the warfarin group and 3.05%/year with administration of dosage-adjusted edoxaban at 30 mg once daily. In addition, even if analysis is restricted to subjects aged 80 years or older in the ENGAGE AF-TIMI 48 study, the annual incidence of major bleeding was 1.99%/year

with administration of edoxaban 15 mg once daily, 6.77%/year in the warfarin group, and 4.28%/year with administration of dosage-adjusted edoxaban at 30 mg once daily, showing that even in elderly patients with AF, the bleeding risk from administration of edoxaban at 15 mg once daily is lower than that of warfarin or of edoxaban at the approved dosage.

Thus, administration of edoxaban at 15 mg once daily is associated with a lower bleeding risk than the available oral anticoagulant warfarin or administration of edoxaban at 30 mg or 60 mg once daily, and from the efficacy standpoint, it is considered to be effective at reducing the risk of stroke to a certain extent. Therefore, it is considered that 15 mg of edoxaban once daily can be administered to elderly patients with AF who have not received aggressive anticoagulant therapy due to concerns about bleeding.

Accordingly, we planned a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of administration of edoxaban at 15 mg once daily in elderly patients with NVAF who are ineligible for the standard of care, oral anticoagulants, at the approved dosage[§] due to concerns about bleeding. A composite of stroke and SEE was selected for primary efficacy endpoint, to evaluate the superiority of administration of edoxaban at 15 mg once daily in reducing the risk of stroke and SEE compared to the placebo group. Major bleeding was selected for the primary safety endpoint, and compared with the placebo group, and clinical acceptability was also assessed with reference to the incidence of major bleeding with available oral anticoagulant therapies. If this study finds that administration of edoxaban at 15 mg once daily is effective, and that its safety is clinically acceptable, it is expected to provide a new option for stroke prevention in elderly patients with NVAF who have not received aggressive treatment with standard of care.

2. STUDY OBJECTIVES

To evaluate the efficacy and safety of 15 mg of DU-176b in patients with NVAF aged 80 years or older who are ineligible for available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the approved dosage.[**] To evaluate the superiority of 15 mg of DU-176b compared to placebo in a composite endpoint of stroke and SEE as the primary efficacy endpoint.

[§]: INR controlled at between 1.6 and 2.6 with warfarin

[**]: For warfarin, INR controlled at between 1.6 and 2.6

3. STUDY DESIGN

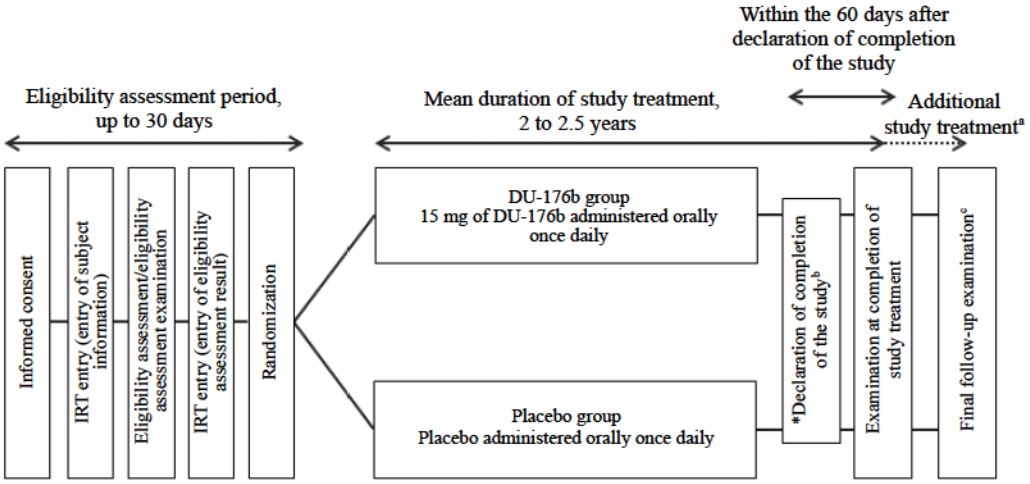
The efficacy and safety of 15 mg of DU-176b once daily will be evaluated in a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven study in patients with NVAF aged 80 years or older who are ineligible for available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the approved dosage.**

The workflow from informed consent to the final follow-up examination is shown in Figure 3-1.

The investigator or subinvestigator will obtain consent from potential subjects for this study and then enter their subject information into interactive response technology (IRT). Within 30 days after informed consent, an eligibility assessment examination will be performed to determine whether or not the subjects meet all inclusion criteria and exclusion criteria, and the eligibility assessment results for the subjects will be entered into IRT. Subject enrolled in IRT will be assigned randomly to the DU-176b group or placebo group in a 1:1 ratio.

After randomization, study treatment will be started on the same date that notification of study drug identifiers is given. Completion of the study will be declared when the planned number of subjects with primary efficacy endpoint events (stroke and SEE) has been collected. Administration of the study drug will be continued until the examination at completion of study treatment performed within 60 days after the declaration of completion of the study. When the investigator or subinvestigator requires to know the study treatment assignment for each subject to determine the subsequent treatment after the final administration of the study drug, the study treatment can be continued until the final follow-up examination after obtaining consent from the subject. The final follow-up examination will be performed in the subjects, in principle, within a month after notifying their study treatment assignments.

Figure 3-1 Study Design



a: Subjects who provided consent will continue to receive the study treatment. The planned duration of the additional study treatment is 3 to 4 months.
b: Completion of the study will be declared when the planned number of subjects with primary efficacy endpoint events has been collected.
c: For subjects who do not continue the study treatment, the final follow-up examination will be performed within 30 to 37 days after the examination at completion of study treatment.
For subjects who continue the study treatment, the final follow-up examination will be performed, in principle, within a month after notifying their study treatment assignments.

<Rationale>

The objective of administering oral anticoagulant therapy to patients with NVAF is to reduce the risk of thromboembolisms such as stroke or SEE, and clinical studies of anticoagulant therapy in patients with NVAF generally use the occurrence of stroke and SEE as efficacy endpoints. To assess the incidence of clinical events such as these, it is necessary to collect a certain number of subjects with efficacy events, and therefore this study will be conducted as an event-driven study. As there is no specification about the period for which it is necessary to reduce the risk of thromboembolism in patients with NVAF, the duration of study treatment for each subject will not be specified, and instead the study treatment will be continued until the visit directly after completion of the study is declared, when the required number of efficacy events have been collected.
The study subjects are patients with NVAF with a high risk of stroke but who have not received oral anticoagulants (non-VKA oral anticoagulants or warfarin) due to concerns about bleeding, or who are receiving warfarin at an anticoagulant strength not

recommended in the guidelines.[††] For this reason, it is not possible to use warfarin or non-VKA oral anticoagulants at the approved dosage[‡‡] as a control. Antiplatelet drugs are also unsuitable as the control in this study, since they are not the standard of care for reducing the risk of stroke in patients with AF, and antiplatelet therapy in patients with AF is not recommended. Thus, as it is not feasible to select a specific medication as a control drug, we have decided to use a placebo as a control to evaluate the efficacy and safety of administration of 15 mg of DU-176b once daily. To minimize subject selection bias, we have decided to conduct randomization after the eligibility of subjects has been determined, and to minimize treatment bias and assessment bias, we have selected double-blinding as the blinding level. The clinical events selected as efficacy and safety endpoints will be assessed under blinded conditions by event assessment committees independent of the investigators and Sponsor.

[††]: INR controlled at below 1.6

[‡‡]: For warfarin, INR controlled at between 1.6 and 2.6

4. STUDY POPULATION

4.1 Selection of Subjects

Subjects who meet all of the following inclusion criteria and exclusion criteria, and provide written consent of their own free will, will be selected. In the case of patients with concurrent dementia who are unable to provide written consent in person, written approved consent from a legally acceptable representative will be mandatory (see "15.3 Informed Consent").

4.1.1 Inclusion Criteria

1) Patients with NVAF with history of AF documented by any electrical tracing within the 1 year prior to the day of informed consent
2) Patients with at least 2 of the following thromboembolism risk factors ($CHADS_2$ index score ≥ 2)
   i) Congestive heart failure
   ii) Hypertension
   iii) Age ≥ 75 years
   iv) Diabetes mellitus
   v) History of transient ischemic attack (TIA) or cerebral infarction (excluding occurrences within the 30 days prior to the day of randomization)
3) Patients with aged ≥ 80 years on the day of informed consent
4) Patients who are ineligible[§§] for available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the approved dosage,[***] and with at least 1 of the following bleeding risks:
   i) Severe renal impairment (creatinine clearance [CLcr] calculated by the Cockcroft-Gault formula ≥ 15 mL/min and < 30 mL/min)
   ii) History of bleeding from critical area or organ (such as intracranial, intraocular, or gastrointestinal bleeding)
   iii) Low body weight (≤ 45 kg)
   iv) Continuous use of acidic non-steroidal anti-inflammatory drugs (NSAIDs)
   v) Patients using 1 antiplatelet drug (for a purpose other than prophylaxis of

[§§] Subjects such as those not eligible for continued administration at the approved dosage for the drug due to concerns about bleeding risk, or those who have not been administered available oral anticoagulants at the approved dosage but are expected to have a high bleeding risk from available oral anticoagulants at the approved dosage.
[***]: For warfarin, INR controlled at between 1.6 and 2.6

cardioembolic stroke)

<Rationale>
The study subjects are elderly patients with NVAF aged ≥ 80 years who are ineligible for oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the approved dosage.*** The study will enroll the patients with NVAF diagnosed by their physician to be ineligible to receive treatment with available oral anticoagulants at the approved dosage after consideration of the bleeding risk from administration of warfarin, and also consideration of bleeding risk in accordance with the precautionary text in the Warnings section of the package inserts for non-VKA oral anticoagulants stating "when using this drug, a careful consideration should be given to whether administration of this drug is appropriate, taking bleeding risk into consideration."

1) To ensure that the patient is an AF patient.
2) A $CHADS_2$ index score ≥ 2, at which level all available oral anticoagulants are recommended in the Guidelines for Pharmacotherapy of Atrial Fibrillation, [6)] was selected.
3) Patients with aged ≥ 80 years[8)] were selected, since patients of this age account for at least half of the patients with NVAF for whom anticoagulant therapy is recommended but who do not receive anticoagulants despite being at particularly high risk from stroke.
4) Renal impairment, low body weight, and concomitant administration of antiplatelet drugs are considered to be factors related to the occurrence of major bleeding during anticoagulant therapy. [6)] Bleeding such as intracranial, intraocular, intrathecal, retroperitoneal, or intraarticular bleeding, or a history of bleeding from critical areas or organs such as gastrointestinal tract bleeding[19),20),21)] or concomitant administration of acidic NSAIDs[22)] are considered to be factors for bleeding risk.

4.1.2 Exclusion Criteria

1) Transient AF secondary to other reversible disorders (e.g. thyrotoxicosis, cardiac or thoracic surgery, pneumonia, severe anemia)
2) Patients who received warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban within the 8 weeks prior to the day of randomization
3) Patients receiving warfarin with INR controlled at ≥ 1.6 in 2 of the 3 most recent examinations, including the eligibility assessment examination, measured at least 4 weeks apart (patients with INR ≥ 1.6 at the eligibility assessment examination are

excluded)

4) Patients with particularly high bleeding risk meeting any of the following criteria:
   i) Active bleeding on the day of informed consent*
      *: Subcutaneous bleeding will be included if there is at least 1 hematoma with a maximal diameter of at least 5 cm, and urinary findings will be included if frank hematuria is observed.
   ii) Unresolved peptic ulcer on the day of informed consent
   iii) Hemoglobin < 9 g/dL, or platelet count < $10 \times 10^4/\mu L$ at the eligibility assessment examination
   iv) Hereditary hemorrhagic disease
5) Cerebral infarction or TIA within the 30 days prior to the day of randomization
6) Patients with rheumatic valve disease
7) History of prosthetic valve replacement (mechanical or biological valves)*
   *: History of mitral valve repair is allowed in the study.
8) Patients with infective endocarditis
9) Patients with atrial myxoma
10) Observed presence of left ventricular or atrial thrombus
11) Observed hereditary thrombophilia
12) Patients with scheduled electrical or pharmacologic defibrillation between the day of informed consent and the time of the examination at completion of study treatment
13) Uncontrolled hypertension (systolic blood pressure persistently > 160 mmHg or diastolic blood pressure persistently > 100 mmHg)
14) CLcr calculated by the Cockcroft-Gault formula < 15 mL/min
15) Patients who have started hemodialysis or who may start hemodialysis by the time of the examination at completion of study treatment
16) Patients receiving dual antiplatelet therapy (e.g., aspirin plus a thienopyridine) at the time of informed consent, or those expected to receive dual antiplatelet therapy after the time of informed consent, who cannot safely discontinue use of either of the antiplatelet drugs
17) Patients with hepatic function disorder accompanied by coagulation disorder
18) History of acute myocardial infarction (MI) within the 30 days prior to the day of randomization
19) Serious heart disease such as cardiac failure with New York Heart Association (NYHA) classification ≥ 3 or unstable angina pectoris
20) Patients who currently have malignancy. Patients diagnosed with malignancy within the 2 years prior to the day of informed consent, or who have received

treatment with cancer therapy (drugs, radiation, and/or surgery) within the 2 years prior to the day of informed consent, except for patients with adequately treated basal cell carcinoma of the skin, resected squamous cell carcinoma of the skin, and cervix carcinoma in situ.

21) History of receiving any other study drugs within the 60 days prior to the day of informed consent

22) Patients the investigator or subinvestigator considers ineligible

<Rationale>

1 to 3) To select eligible subjects for this study.

4) Due to the possibility of an increased risk of major bleeding from the study treatment.

5 to 11) Due to the markedly high risk of thromboembolism.

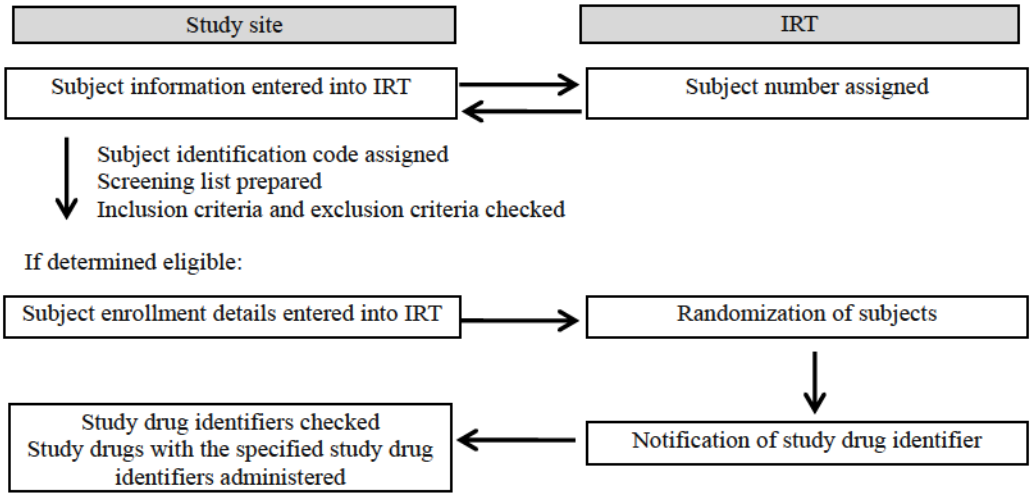
12 to 22) To ensure the safety of subjects and to conduct this study appropriately.

4.1.3 Subject Enrollment

4.1.3.1 Workflow of Subject Enrollment

Subjects will be enrolled in the study using IRT, including IWRS, using the Internet. The enrollment procedure for subjects is shown in Figure 4.1-1.

Figure 4.1-1 Enrollment Procedure for Subjects



After obtaining written informed consent from the subjects (or legally acceptable representatives), the investigator or subinvestigator will assign subject identification codes and prepare a subject screening list, and assess the eligibility of subjects, within

30 days.
The investigator or subinvestigator will enter the required items for all subjects from whom consent has been obtained (including consent from legally acceptable representatives) into IRT. The IRT will assign study-specific subject numbers.
Next, the investigator or subinvestigator will enter the eligibility assessment results for the subjects into IRT. The day of enrollment is defined as the date entered into IRT as the date when eligibility was determined. The day of withdrawal is defined as the date entered into IRT as the date when ineligibility was determined. IRT will perform randomization on the enrolled subjects and assign them study drug identifiers.
The investigator or subinvestigator will confirm the study drug identifiers displayed in IRT and then administer the study drugs marked with those study drug identifiers, on the same date notification of study drug identifiers is given.
If the investigator or subinvestigator determined that a subject is ineligible, the investigator or subinvestigator will explain the reason for this to the subject (or legally acceptable representative) and administer regular treatment. If there are any subjects from whom consent was obtained but who were determined ineligible, the investigator or subinvestigator will enter the fact that these subjects are ineligible in the subject screening list. If the investigator or subinvestigator later determines that a subject is eligible for this study, the investigator or subinvestigator will obtain written consent from the subject (or legally acceptable representative) again, and enroll the subject according to the procedure specified in this section.

4.1.3.2 If Notification Is Received That the Subject Is Receiving Treatment from Another Physician

The investigator or subinvestigator will find out whether or not subjects from whom consent was received are receiving treatment from another physician (another department at the study site or another medical institution). If a subject is receiving treatment from another physician, the investigator or subinvestigator will notify the other physician that the subject is participating in the clinical study, with the consent of the subject (or legally acceptable representative). The fact that this notification has been given will be recorded, for example in medical records.

4.2 Individual Subject Interruption or Discontinuation of Study Drug, Individual Subject Discontinuation of Study Participation, and Termination of the Entire Study

4.2.1 Study Drug Interruption

4.2.1.1 Interruption and Resumption of Study Drug

If systolic blood pressure persistently exceeds 160 mmHg or diastolic blood pressure persistently exceeds 100 mmHg on the same day, study treatment for the relevant subject will be promptly interrupted. After treatment is temporarily interrupted, repeat measurements will be made at least one week apart, and if it is found that the above conditions are not met, the study treatment will be resumed.

The study treatment may be temporarily interrupted at the discretion of the investigator or subinvestigator, for example due to the occurrence of an adverse event or invasive treatment or tests being performed. Except in emergencies, surgery or invasive treatment or tests will be performed when at least 24 hours have passed since study treatment. To determine whether or not study treatment can be resumed before the examination at completion of study treatment, the investigator or subinvestigator will assess the subject's clinical state within the 7 days after the study drug interruption, and at least every 8 weeks thereafter. If the investigator or subinvestigator determines that the study treatment can be resumed, and the subject (or legally acceptable representative) consents to this, the study treatment will be resumed, and the study procedures at the specified visit directly after resumption will also be resumed. If the study treatment has not been resumed at the time of the examination at completion of study treatment, it will be considered that study treatment has been discontinued at this point.

If the study treatment is interrupted, the investigator or subinvestigator will enter the duration of study drug interruption, the reason for interruption, and whether or not the study treatment can be resumed on the case report form. If the study treatment is interrupted due to an adverse event, the investigator or subinvestigator will enter information on the case report form in accordance with "9.4 Adverse Event Information to Be Reported" and "9.6 Action When an Adverse Event Occurs."

4.2.1.2 Follow-up Survey During Study Drug Interruption

The investigator or subinvestigator will survey the following items until the examination at completion of study treatment or until the resumption of treatment at the visit specified in "6. STUDY PROCEDURES" at least every 8 weeks at a visit or by telephone, and will enter the information on the case report form. If the subject cannot be contacted by

telephone, surveys will be performed by letter.

1) Whether any serious adverse events have occurred
2) Whether any efficacy events have occurred
3) Whether any bleeding events have occurred
4) Whether any of the following drugs (including over-the-counter drugs) have been used: anticoagulants, thrombolytic drugs, antiplatelet drugs, intravenous antiarrhythmic drugs, or acidic NSAIDs
5) Blood pressure and pulse rate (only if the subject makes a visit)
6) Laboratory tests determined to be appropriate by the investigator or subinvestigator (only if the subject makes a visit). However, if warfarin is being administered, measurement of PT-INR is mandatory.

4.2.2 Study Drug Discontinuation

4.2.2.1 Study Drug Discontinuation Criteria

If a subject meets any of the following criteria, the investigator or subinvestigator will promptly discontinue the study treatment of the relevant subject, and take suitable action in response. As far as possible, the investigator or subinvestigator will perform the examination at discontinuation and make every attempt to ensure the safety of the subject, and will enter the reason for discontinuation on the case report form.

1) If hemodialysis is started
2) If the subject refuses to receive the study drug, or the legally acceptable representative refuses to allow the subject to receive the study drug, based on a request made of his/her own free will (if consent is given for the follow-up survey specified in "4.2.2.2 Follow-up Survey After Study Drug Discontinuation" after study drug discontinuation, the follow-up survey will be performed)
3) If the study treatment is interrupted and is not resumed by the time of the examination at completion of study treatment
4) If the investigator or subinvestigator determines that the study treatment should be discontinued for any other reason

In the case of subjects who meet criterion 2) above (withdrawal of consent for the study treatment), if consent to resume the study treatment at the free will of the subject (or legally acceptable representative) is obtained before the examination at completion of study treatment, and the investigator or subinvestigator considers that there are no problems with the subject's clinical state, the study treatment may be resumed. If the

study treatment is resumed, the study procedures at the specified visit directly after resumption will be performed.

4.2.2.2 Follow-up Survey After Study Drug Discontinuation

The investigator or subinvestigator will survey the following items until the examination at completion of study treatment at least every 8 weeks at a visit or by telephone, and will enter the information on the case report form. If the subject cannot be contacted by telephone, surveys will be performed by letter. In the case of subject meeting "4.2.2.1-2) Study Drug Discontinuation Criteria" (withdrawal of consent for the study treatment), the investigator or subinvestigator will also find out whether the subject (or legally acceptable representative) is willing to resume the study treatment, and will enter the results on the case report form.

1) Whether any serious adverse events have occurred
2) Whether any efficacy events have occurred
3) Whether any bleeding events have occurred
4) Whether any of the following drugs (including over-the-counter drugs) have been used: anticoagulants, thrombolytic drugs, antiplatelet drugs, intravenous antiarrhythmic drugs, or acidic NSAIDs
5) Blood pressure and pulse rate (only if the subject makes a visit)
6) Laboratory tests determined to be appropriate by the investigator or subinvestigator (only if the subject makes a visit). However, if warfarin is being administered, measurement of PT-INR is mandatory.

4.2.3 Discontinuation of Study Participation and Termination of the Entire Study

4.2.3.1 Discontinuation of Study Participation Due to Withdrawal by Subject

If a subject (or legally acceptable representative) makes a request to withdraw not only from receiving the study drug but also from participation in the study, including all study procedures or follow-up survey related to the study, the investigator or subinvestigator will promptly withdraw the relevant subject from the study and take the suitable action for the subject in response. The investigator or subinvestigator will also perform the examination at discontinuation and make every attempt to ensure the safety of the subject as far as the subject (or legally acceptable representative) is willing to cooperate, and will enter the date of discontinuation and the reason for discontinuation on the case report form.

4.2.3.2 Discontinuation of Study Participation in the Event of a Major Protocol Deviation

In the event of a major deviation (a situation where it is not feasible to continue the study safely) relating to a subject, the investigator or subinvestigator will promptly withdraw the relevant subject from the study and take the suitable action for the subject in response. The investigator or subinvestigator will perform follow-up survey of abnormal findings at the time of discontinuation, and as far as the subject (or legally acceptable representative) is willing to cooperate, will perform the examination at discontinuation and make every attempt to ensure the safety of the subject, and will enter the date of discontinuation and the reason for discontinuation on the case report form.

4.2.3.3 Discontinuation of Study Participation Due to the Death of a Subject

If a subject dies, the subject will be deemed to have been withdrawn from study participation at the time of death. The investigator or subinvestigator will survey information such as the date and time of death and the reason for the death according to "6.14 Efficacy Events" and enter the information on the case report form.

4.2.3.4 Termination of the Entire Study by Sponsor

If the Sponsor decides to terminate the entire study according to the regulations specified in "15.8.1 Termination or Interruption of the Study," the investigator or subinvestigator will promptly withdraw subjects from the study and take the suitable action for subjects in response. The investigator or subinvestigator will perform follow-up survey of abnormal findings at the time of discontinuation, and as far as the subjects (or legally acceptable representatives) are willing to cooperate, will perform the examination at discontinuation and make every attempt to ensure the safety of subjects, and will enter the date of discontinuation and the reason for discontinuation on case report forms.

5. METHODOLOGY

5.1 Study Drug

Details of the study drug and how to handle it are available in the Investigator's Brochure and Study Drug Management Procedures.

5.1.1 Investigational Product

1) Code name: DU-176b
2) Generic name: edoxaban tosilate hydrate

3) Content and dosage form: Yellow film-coated tablets containing 15 mg of edoxaban per tablet
4) Lot number: Please refer to the Study Drug Management Procedures

5.1.2 Placebo

1) Content and dosage form: Yellow film-coated tablets not containing any active ingredient, with an appearance (shape, color, and odor) indistinguishable from that of the Investigational Product
2) Lot number: Please refer to the Study Drug Management Procedures
3) Provider: Daiichi Sankyo Co., Ltd.

5.1.3 Labeling and Packaging

The packaging of the study drug and the contents of labels are shown in the Study Drug Management Procedures.

5.1.4 Study Drug Accountability

After concluding a study contract, the Sponsor will dispense the study drug to the study site. The study drug managers will store the drug at room temperature and manage it. Management and collection of the study drug will be performed according to the Study Drug Management Procedures.

5.2 Study Treatments Administered

5.2.1 Dose and Route of Administration

After randomization, study treatment will be started on the same date that notification of study drug identifiers is given. One tablet of DU-176b 15 mg or placebo will be administered orally once daily. Administration of the study drug will be continued until the examination at completion of study treatment performed within 60 days after the declaration of completion of the study. Completion of the study will be declared when the planned number of subjects with primary efficacy endpoint events (stroke and SEE) has been collected. The planned mean duration of study treatment is 2 to 2.5 years. When the investigator or subinvestigator requires to know the study treatment assignment for each subject to determine the subsequent treatment after the final administration of the study drug, the study treatment can be continued until the final follow-up examination (in principle, within a month after notifying their study treatment assignments) after obtaining consent from the subject. The planned duration of the additional study

treatment from the examination at completion of study treatment to the final follow-up examination is 3 to 4 months.

<Rationale>
For the DU-176b group, a dosage of 15 mg once daily was selected, so that it is expected to be effective at reducing the risk of stroke, and so that the bleeding risk is lower than that for the approved edoxaban dosage.
In a phase 3 global study of DU-176b in patients with NVAF (ENGAGE AF-TIMI 48), the annual incidence of composite of stroke and SEE with administration of edoxaban at 15 mg once daily was 2.36%/year for the overall population and 2.79%/year for the Japanese population (2.21%/year and 1.20%/year respectively, in the warfarin group). At present, due to changes in the medical environment, the incidence of events such as these may have decreased, but in meta-analysis using data from randomized clinical studies of VKAs conducted in patients with AF in the past, it was reported that the annual incidence of non-fatal stroke in the control group (untreated) was 7.6%/year (2.5%/year in the VKA group). Given this, from the results of the ENGAGE AF-TIMI 48 study, it is expected that even if edoxaban is administered at 15 mg once daily, it will be effective at reducing the risk of stroke to a certain extent, based on its anticoagulant effect. The annual incidence of composite of stroke and SEE during administration of edoxaban at 15 mg once daily in subjects aged 80 years or older in the ENGAGE AF-TIMI 48 study was 2.33%/year for the overall study population, which is similar to the result (2.36%/year) for all subjects administered 15 mg once daily regardless of age. In addition, in the AVERROES study[16] evaluating the efficacy of apixaban in patients with AF and VKA is not indicated, the annual incidence of composite of stroke and SEE in the aspirin group, which was the control group, was 3.7%/year, and thus the annual incidence during administration of edoxaban at 15 mg once daily in the ENGAGE AF-TIMI 48 study was lower than this. Aspirin is not positioned as a standard of care for reducing the risk of stroke in patients with AF, and is not recommended as antithrombotic therapy in patients with AF[6], but it is expected that administration of edoxaban at 15 mg once daily will show a greater reduction of the risk of stroke than aspirin.
From the safety standpoint, no hemorrhagic stroke was found during administration of edoxaban at 15 mg once daily in the ENGAGE AF-TIMI 48 study, and the annual incidence of intracranial hemorrhage was 0.14%/year, lower than the incidence in the warfarin group of 1.26%/year, and also lower than the incidence of 0.57%/year in subjects administered edoxaban at 30 mg once daily due to dosage adjustment. The

annual incidence of major bleeding was 1.50%/year with administration of edoxaban at 15 mg once daily, which was lower than the incidences of 4.85%/year in the warfarin group and 3.05%/year with administration of dosage-adjusted edoxaban at 30 mg once daily. In addition, even if analysis is restricted to subjects aged 80 years or older in the ENGAGE AF-TIMI 48 study, the annual incidence of major bleeding was 1.99%/year with administration of edoxaban 15 mg once daily, 6.77%/year in the warfarin group, and 4.28%/year with administration of dosage-adjusted edoxaban at 30 mg once daily, showing that even in elderly patients with AF, the bleeding risk from administration of edoxaban at 15 mg once daily is lower than that of warfarin or of edoxaban at the approved dosage.
Thus, administration of edoxaban at 15 mg once daily is associated with a lower bleeding risk than the available oral anticoagulant warfarin or administration of edoxaban at 30 mg or 60 mg once daily, and from the efficacy standpoint, it is considered to be effective at reducing the risk of stroke to a certain extent. Therefore, administration at 15 mg once daily was selected as the dosage in the DU-176b group of this study.

5.2.2 Randomization and Blinding

5.2.2.1 Method of Assigning Subjects to Treatments

An independent biostatistician will prepare a randomization schedule in accordance with the Sponsor's directions. Based on the information entered into IRT, subjects will be assigned to the DU-176b group or placebo group in a 1:1 ratio using a stratified randomization method with the $CHADS_2$ index score (≤ 2 points, ≥ 3 points) as a factor.

5.2.2.2 Blinding

This study will be a double-blind study, and blinding will be performed for all related parties (subjects, investigators, and the Sponsor) other than the independent biostatistician, those involved in assignment and packaging of the study drug and quality assurance, and those relating to the drug concentration measurement laboratory.

5.2.2.3 Unblinding Procedure for Emergencies

5.2.2.3.1 If the Investigator or Subinvestigator Considers That Unblinding Is Absolutely Necessary

If the investigator or subinvestigator considers that information on which treatment group a subject belongs to is absolutely necessary to treat an adverse event, the investigator or subinvestigator will unblind using IRT.

5.2.2.3.2 If a Serious Adverse Event Occurring in This Study Is Reported to the Regulatory Authority

The assigned person for limited unblinding of safety information will unblind using IRT.

5.2.2.4 Unblinding Procedure

When items 1), 2), and 3) below have been checked and it has been considered that there are no problems, the Sponsor will unblind.

1) The database has been locked.
2) The analysis plan has been finalized.
3) The decisions on whether or not to include subjects in analysis sets and on the handling of data have been finalized.

5.3 Prohibited Concomitant Medications and Prohibited Tests

5.3.1 Prohibited Concomitant Medications

Between the time of informed consent and the final dose of study drug (excluding the follow-up survey periods during study drug interruption and after study drug discontinuation), concomitant administration of anticoagulants or thrombolytic drugs will be prohibited. Mono antiplatelet therapy (including over-the-counter drug containing aspirin) will be permitted only when administered to treat concurrent diseases, but concomitant administration of antiplatelet therapy to reduce the risk of cardioembolic stroke based on AF will be prohibited.
If it becomes necessary to administer prohibited concomitant medications after the initiation of study treatment, the treatment will be interrupted (see "4.2.1 Study Drug Interruption").

<Rationale>
Concomitant administration of anticoagulants, antiplatelet drugs to reduce the risk of cardioembolic stroke based on AF, and thrombolytic drugs has been prohibited in this study because these drugs will affect the efficacy assessment of the study drug. As concomitant administration of dual or multidrug antiplatelet therapy causes a particularly large increase in bleeding risk, it has also been prohibited, to ensure the safety of subjects.

5.3.2 Prohibited Tests

To ensure blinding, tests affecting blinding will be prohibited at the study site from the initiation of study treatment until 2 days after the day of the examination at completion of study treatment (excluding the duration of follow-up at least 3 days after the date of study drug discontinuation or the date of study drug interruption) or the final follow-up examination (when the study treatment is continued after the examination at completion of study treatment), such as the following: pharmacodynamic (PD) indicator tests (prothrombin time [PT], activated partial thromboplastin time [aPTT]), and biomarker tests (D-dimer, prothrombin fragment 1+2 [F1+2], activated coagulation factor X [Xa]). However, cases where testing is unavoidable, for example to treat an adverse event or in an emergency, will be permitted. Whether PD and biomarker tests were performed during the period from the initiation of study treatment to the day of the examination at completion of study treatment, the date of conduction of these tests, and the concerned test items will be recorded on case report forms.

6. STUDY PROCEDURES

6.1 Study Procedure and Specimen Collection Schedule

The timing of study procedures and specimen collection in this study is shown in Table 6-1. The investigator or subinvestigator will record information such as the results of study procedures, the dates and times of specimen collection, the state of specimens at the time of sampling, and comments about these.

The examination at completion of study treatment will be performed within 60 days after the declaration of completion of the study, including subjects for whom study treatment has been interrupted or discontinued. Completion of the study will be declared when the planned number of subjects with primary efficacy endpoint events (stroke and SEE) has been collected.

The final follow-up examination will be performed within the 30 to 37 days after the examination at completion of study treatment. For subjects who continue the study treatment after the examination at completion of study treatment, the final follow-up examination will be performed, in principle, within a month after notifying their study treatment assignments.

Follow-up survey of subjects for whom study treatment has been interrupted or discontinued will be performed according to "4.2.1.2 Follow-up Survey During Study Drug Interruption" and "4.2.2.2 Follow-up Survey After Study Drug Discontinuation" respectively.

Surveys of subjects for whom "4.2.3 Discontinuation of Study Participation and Termination of the Entire Study" applies will be deemed complete as of the examination at discontinuation, which will be performed as far as is possible.

Table 6-1 Study Procedure and Specimen Collection Schedule

	Eligibility assessment examination		Duration of study treatment			Final follow-up examination[b]
			Every 4 weeks from Week 4 to Week 48	Every 8 weeks from Week 48 onward	Examination at completion of study treatment[a] /examination at discontinuation	
Visit	0	1	2–13	14–		
Visit window	Within the 30 days prior to randomization[c]		±14 days[c]	±14 days[c]	Within the 60 days after declaration of completion of the study[c] Within the 7 days after discontination[c]	Within the 30 to 37 days after the examination at completion of study treatment[c]
Informed consent	X					
IRT entry (entry of subject information)	X					
Baseline subject characteristics[d]	← X →					
IRT entry (entry of eligibility assessment result), randomization		X				
Study drug administration	←	→	←	→	→ [e]	[f]
Study drug compliance	←	→	←	→	→	
Height	← X →					
Physical examination/medical interview	← X →		X	X	X	X
Body weight	← X →		X	X	X	X
Blood pressure/pulse rate	← X →		X	X	X	X
Hematology test[g]	← X →		X[h]	X	X	X
Blood chemistry test[g]	← X →		X[h]	X	X	X
Endocrinology test[g]	← X →		X[h]	X	X	X
Urinalysis[g]	← X →		X[h]	X	X	X
CLcr[i]	← X →		X[h]	X	X	X
12-lead electrocardiogram (ECG)	← X →		X[j]	X[k]	X	X
Head CT or MRI[l]	← X →					
Whether surgery or hospitalization occurred	←	→	←	→	→	
Adverse events	←	→	←	→	→	→ [m]
Efficacy/bleeding events	←	→	←	→	→	
Concomitant medication	←	→	←	→	→	
Follow-up survey after interruption/discontinuation of study drug[n]			←	→	→	
Pharmacokinetic blood sampling[g]			X[o]			
Blood sampling for PD indicators[g]		X				
Blood sampling for biomarker measurement[g]		X	X[o]			
PGx banking[p]			← X[q] →			

a: Will not be performed on subjects withdrawn from the study.
b: Will be performed in subjects who continue the study treatment, in principle, within a month after notifying their study treatment assignments.
c: Will be calculated by taking the date of the scheduled visit to be Day 0.
d: Falling score, frailty assessment, and one-leg standing test with eyes open will be surveyed by the time of Visit 3.
e: Study treatment will be started on the same date that notification of study drug identifiers is given. Study treatment will be continued until the examination at completion of study treatment, which will be performed within the 60 days after the declaration of completion of the study that is made when the planned number of subjects with primary efficacy endpoint events (stroke and SEE) has been collected.
f: The study drug will be administered only to subjects who provided consent for the additional study treatment during the period from the examination at completion of study treatment to the final follow-up examination.
g: These will be measured at the central laboratory.
h: Will be performed once every 8 weeks (Week 4 to Week 48: Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, Visit 13/Week 48 onward: Visit 14, Visit 15, Visit 16...).
i: Will be calculated with the Cockcroft-Gault formula.
j: Will be performed once every 12 weeks (Visit 4, Visit 7, Visit 10, Visit 13).
k: Will be performed once every 24 weeks (Visit 16, Visit 19, Visit 22...).
l: If this is performed within 4 weeks before the day of informed consent as part of a physical examination, the results may be used for the eligibility assessment examination, with the consent of the subject.
m: During the period from the examination at completion of study treatment to the final follow-up examination, only serious adverse events will be monitored.
n: Checks on whether serious adverse events have occurred, whether efficacy events have occurred, whether bleeding events have occurred, whether the following drugs have been used: anticoagulants, thrombolytics, antiplatelet drugs, intravenous antiarrhythmics, and acidic NSAIDs, blood pressure/pulse rate (if the subject has made a visit), and laboratory tests determined to be appropriate by the investigator or subinvestigator (if the subject has made a visit. If warfarin is being used, measurement of PT-INR is mandatory) will be conducted every 8 weeks.
o: Will be performed on Visit 3.
p: Will be performed only at study sites where it is possible.
q: Will be performed from Visit 2 onwards.

6.2 Baseline Subject Characteristics

Between the day of informed consent (Visit 0) and randomization, the following baseline subject characteristics will be surveyed and entered on case report forms.

1) Date of informed consent, date of enrollment, subject number, and study drug identifier
2) Demographic
   Date of birth, age (at consent), sex, and alcohol use
3) Variables relating to disease and prognosis
   Type of AF, risk factors for thromboembolism ($CHADS_2$ index score and CHA_2DS_2-VASc index score[6]) (whether present or not and details), HAS-BLED score[6] (whether present or not and details), medical history (whether present or not and details), inpatient/outpatient status, history of administration of oral

anticoagulants (whether present or not and details), bleeding risk (whether present or not and details), PT-INR,* whether certified as requiring nursing care and grade of care required, falling risk (whether present or not and details), the following items will be surveyed by Visit 3 (see Appendix): falling score,[23] frailty assessment,[24),25] one-leg standing test with eyes open [26]

*: If the subject was receiving warfarin before informed consent was received

6.3 Study Drug Compliance

From the initial dose of study drug date (the same date as the date of notification of the study drug identifier) to the examination at completion of study treatment or the examination at discontinuation,††† medical interviews will be performed and study drug compliance (number of tablets administered) will be determined from the remaining drug collected from subjects. The following information will be entered on case report forms: whether study treatment was administered, the date of the start of treatment, the date of completion of treatment, whether study drug interruption occurred, date of study drug interruption, date of study drug resumption, and the reasons for study drug interruption.

6.4 Concomitant Medications (Including Over-the-counter Drugs)

The following information about concomitant medications and drugs used to treat adverse events from the time of informed consent (Visit 0) to the examination at completion of study treatment or the examination at discontinuation†††: whether drugs were used, drug names, duration of treatment, and reason for use. If prohibited concomitant medications, intravenous antiarrhythmic drugs, P-glycoprotein (P-gp) inhibitors, or acidic NSAIDs were administered, the dose and route will also be entered on case report forms in addition to the above.

In the duration of follow-up during study drug interruption and after study drug discontinuation, whether the following drugs have been used will be surveyed at least every 8 weeks, and if they have, the same information will be surveyed as in the case where drugs such as prohibited concomitant medications were used, and entered on the case report form.

- Anticoagulants, thrombolytic drugs, antiplatelet drugs, intravenous antiarrhythmic drugs, acidic NSAIDs

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†††: For subjects withdrawn from study treatment and subjects withdrawn from study participation

Testing drugs, fluid infusions, fluid supplementation, nutritional formulations, disinfectants, and anesthetics, other than those used for treating adverse events, will not be entered on case report forms.

6.5 Head Imaging

In the eligibility assessment examination, head imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) will be performed. It will be confirmed that there are no findings of active bleeding, and the imaging method, date of imaging, and bleeding findings will be entered on case report forms. However, if imaging is performed within the 4 weeks from the day of informed consent as part of routine care, the results of this imaging may be used to quality the subject, with the subject's consent.

6.6 Twelve-lead Electrocardiogram

Twelve-lead electrocardiography (ECG) will be performed at the eligibility assessment examination, during the study treatment period (once every 12 weeks from Week 4 to Week 48 [Visit 4, Visit 7, Visit 10, and Visit 13], and once every 24 weeks from Week 48 onward [Visit 16, Visit 19, Visit 22...]), at the examination at completion of study treatment, and at the final follow-up examination or the examination at discontinuation‡‡‡, and the date of examination, whether AF was present, and other findings will be entered on case report forms. If any clinically meaningful change compared with the results of the eligibility assessment examination is observed in examinations after the initiation of study treatment, the investigator or subinvestigator will assess whether to handle this change as an adverse event, and if it is considered to be an adverse event, it will be entered in the adverse event field of the case report form.

6.7 Vital Signs

6.7.1 Height

Height will be measured at the eligibility assessment examination, and the date of measurement and results will be entered on case report forms. Body mass index (BMI) will also be calculated using the body weight measured at the eligibility assessment examination.

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‡‡‡: For subjects withdrawn from study treatment and subjects withdrawn from study participation

6.7.2 Body Weight

Body weight will be measured at the eligibility assessment examination, all visits during the study treatment period, the examination at completion of study treatment, and the final follow-up examination or the examination at discontinuation‡‡‡, and the date of measurement and results will be entered on case report forms. If any significant change compared with the eligibility assessment examination is observed in examinations after the initiation of study treatment, the investigator or subinvestigator will assess whether to handle this change as an adverse event, and if it is considered to be an adverse event, it will be entered in the adverse event field of the case report form.

6.7.3 Blood Pressure/Pulse Rate

Systolic blood pressure, diastolic blood pressure, and pulse rate will be measured at the eligibility assessment examination, all visits during the study treatment period, the examination at completion of study treatment, and the final follow-up examination or the examination at discontinuation‡‡‡, and the date of measurement and results will be entered on case report forms.

If the subject makes visits during study drug interruption or after study drug discontinuation, systolic blood pressure, diastolic blood pressure, and pulse rate will be measured at least every 8 weeks, and the dates of measurements and results will be entered on the case report form.

If any significant change compared with the eligibility assessment examination is observed in tests after the initiation of study treatment, the investigator or subinvestigator will assess whether to handle this change as an adverse event, and if it is considered to be an adverse event, it will be entered in the adverse event field of the case report form.

During study treatment, if systolic blood pressure persistently exceeds 160 mmHg or diastolic blood pressure persistently exceeds 100 mmHg on the same day, study treatment for the relevant subject will be promptly interrupted. After treatment is interrupted, repeat measurements will be made at least one week apart, to consider whether study treatment can be resumed (see "4.2.1.1 Interruption and Resumption of Study Drug").

6.8 Laboratory Tests

Blood samples and urine samples for laboratory tests will be collected at the eligibility assessment examination, once every 8 weeks during the study treatment period (from Week 4 to Week 48, at Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, and Visit 13/from Week 48 onward, at Visit 14, Visit 15, Visit 16...), the examination at completion of study

treatment, and the final follow-up examination or the examination at discontinuation.[§§§]
All laboratory tests will be performed as a batch by SRL, Inc.

1) Hematology test
   Red blood cell count, hemoglobin, hematocrit, white blood cell count, white blood cell differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, and PT-INR*
   *: PT-INR will be measured if the subject received warfarin within the 8 weeks prior to the day of informed consent, or if the subject is receiving warfarin during study drug interruption or during the follow-up after study drug discontinuation.
2) Blood chemistry test
   Total protein, albumin, total bilirubin, direct and indirect bilirubin,** AST, ALT, ALP, GGT, LDH, CK, BUN, creatinine, uric acid, Na, K, Cl, total cholesterol, triglyceride
   **: Direct and indirect assays will be performed when total bilirubin ≥ 2 mg/dL
3) Endocrinology tests
   Troponin I, human brain natriuretic peptide (BNP)
4) Urinalysis
   Urine glucose, urine protein, urine blood, urinary sediment (red blood cells)

If the subject makes visits during study drug interruption or after study drug discontinuation, measurement of laboratory test items the investigator or subinvestigator considers suitable (if warfarin is being administered, PT-INR is mandatory) will be requested, and the dates when specimens were collected will be entered on case report forms.
If any abnormal laboratory data (deviations from reference ranges) are observed, the investigator or subinvestigator will assess whether to handle these data as an adverse event, and if they are considered to be adverse events, they will be entered in the adverse event field of the case report form.

6.9 Creatinine Clearance

CLcr will be calculated using the Cockcroft-Gault formula at the eligibility assessment examination, once every 8 weeks during the study treatment period (from Week 4 to Week 48, at Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, and Visit 13/from Week 48 onward, at Visit 14, Visit 15, Visit 16...), the examination at completion of study treatment, and the final follow-up examination or the examination at discontinuation,**** and entered on case report forms. If any significant change compared with the eligibility assessment

§§§: For subjects withdrawn from study treatment and subjects withdrawn from study participation

examination is observed in CLcr after the initiation of study treatment, the investigator or subinvestigator will assess whether to handle this change as an adverse event, and if it is considered to be an adverse event, it will be entered in the adverse event field of the case report form.

Cockcroft-Gault formula
Males: {(140 − age) × body weight (kg)} ÷ {72 × serum creatinine (mg/dL)}
Females: [{(140 − age) × body weight (kg)} ÷ {72 × serum creatinine (mg/dL)}] × 0.85

6.10 Surgery

If a subject receives surgery between the initiation of study treatment and the examination at completion of study treatment or the examination at discontinuation,**** the investigator or subinvestigator will survey information relating to the surgery such as the date of surgery, reason for surgery, amount of blood lost during surgery, and whether blood transfusion was performed, and enter this on the case report form. If the surgery is due to an adverse event, the investigator or subinvestigator will perform a survey according to "9.4 Adverse Event Information to Be Reported" and enter information about the adverse event in the adverse event field of the case report form.

6.11 Hospitalization

If a subject is hospitalized between the initiation of study treatment and the examination at completion of study treatment or the examination at discontinuation,**** the investigator or subinvestigator will survey information relating to the hospitalization such as the date of hospitalization, the reason for hospitalization, and the date of discharge, and enter this on the case report form. If the hospitalization is due to an adverse event, the investigator or subinvestigator will perform a survey according to "9.4 Adverse Event Information to Be Reported" and enter information about the adverse event in the adverse event field of the case report form.

****: For subjects withdrawn from study treatment and subjects withdrawn from study participation

6.12 Plasma Drug Concentration, Pharmacokinetic Indicators, and Biomarkers

6.12.1 Plasma Drug Concentration

6.12.1.1 Blood Sampling Times and Meal Records for Measuring Plasma Drug Concentration

Blood sampling for measurement of plasma drug concentration will be performed on Week 8 (Visit 3) of the study treatment period (see Table 6-2). The investigator or subinvestigator will instruct the subject to make a visit without receiving the morning dose of the study drug, will collect a blood sample at the trough time promptly after the subject makes a visit, and will record the date of blood sampling and time of blood sampling on the case report form. The investigator or subinvestigator will also enter the times when the study drug was administered 2 days before and 1 day before the day of blood sampling, the start times of the meals before and after the study drug was administered on the day before blood sampling, and the start times of the meals before and after the study drug was administered on the day of blood sampling. After this, the subject will receive the study drug at the study site, and a blood sample will be collected 1 to 3 hours after the study drug was administered, and the time when the study drug was administered and the time when the blood sample was collected will be entered on the case report form. If possible, a blood sample will also be collected between 4 and 8 hours after the study drug was administered, and the time when the blood sample was collected will be entered on the case report form.

Table 6-2 Times of Blood Sampling for Measuring Plasma Drug Concentration

Time of blood sampling	Remarks
Trough	Must be collected
Between 1 to 3 hours after the study drug is administered	Must be collected
Between 4 to 8 hours after the study drug is administered	Will be collected if possible

6.12.1.2 Method of Blood Sampling for Measuring Plasma Drug Concentration, Plasma Isolation, and Storage

A quantity of 5 mL of venous blood will be collected using a 5 mL vacuum blood sampling tube containing lithium heparin. Directly after sampling, the blood will be mixed by inversion and cooled. The specimen will be promptly centrifuged for 10 minutes at 1500 × *g*. The plasma will be immediately fractionated into a container for submission, and stored at the study site at no higher than −20°C, protected from light

until it is collected by SRL, Inc. (the process from sampling of intravenous blood to storage will be performed within 1 hour). SRL, Inc. will place the set of specimens stored according to the Sponsor's instructions in a container with dry ice and send it to the drug concentration measurement laboratory (Q^2 Solutions).

6.12.1.3 Measurement of Blood Plasma Concentration (DU-176b Group Only)

The drug concentration measurement laboratory (Q^2 Solutions) will measure the plasma DU-176 concentration promptly after receiving the specimens. The plasma drug concentration will be measured by liquid chromatography tandem mass spectrometry (LC-MS/MS).

6.12.2 Measurement of Pharmacodynamic Indicators and Biomarkers

6.12.2.1 Times of Blood Sampling for Measuring Pharmacodynamic Indicators

At the eligibility assessment examination (Visit 1) and Week 8 of the study treatment period (Visit 3), blood samples for measuring PD indicators (PT and aPTT) will be collected, and the date of sampling and the time of sampling will be entered on the case report form. The timing of the blood sampling in Week 8 of the study treatment period (Visit 3) will be the same as the timing of the blood sampling for measuring plasma drug concentration (see "6.12.1.1 Blood Sampling Times and Meal Records for Measuring Plasma Drug Concentration").

6.12.2.2 Times of Blood Sampling for Measuring Biomarkers

At the eligibility assessment examination (Visit 1) and Week 8 of the study treatment period (Visit 3), blood samples for measuring biomarkers (D-dimer and F1+2) will be collected, and the date of sampling and the time of sampling will be entered on the case report form. The timing of the blood sampling in Week 8 of the study treatment period (Visit 3) will be before the study drug is taken (the trough time).

6.12.2.3 Method of Blood Sampling for Measuring Pharmacodynamic indicators Biomarkers, Plasma Isolation, and Storage

A quantity of 4.5 mL of venous blood will be collected using a single 4.5 mL vacuum blood sampling tube containing citric acid. Promptly after sampling, the plasma will be separated and fractionated into a container for submission, and stored frozen at the study site until it is collected by SRL, Inc.

6.12.2.4 Measurement of Pharmacodynamic Indicators and Biomarkers

Centralized measurement of PD indicators and biomarkers will be performed at SRL, Inc. SRL, Inc. will measure PD indicators (PT and aPTT) and biomarkers (D-dimer and F1+2) promptly after receiving specimens. The results of measurement will not be disclosed to the study site or the Sponsor, except in cases where this is unavoidable, such as when action is taken to treat adverse events or in emergencies.

6.13 Adverse Events

If an adverse event occurs between the initiation of study treatment and the examination at completion of study treatment or the examination at discontinuation,†††† a survey will be performed according to "9.4 Adverse Event Information to Be Reported" and the information will be entered on the case report form.

During study drug interruption and after study drug discontinuation, a survey to find whether any serious adverse events have occurred will be performed at least every 8 weeks, and if they have, a survey will be performed according to "9.4 Adverse Event Information to Be Reported" and the information will be entered on the case report form.

Occurrence of any serious adverse events will be monitored until the final follow-up examination and will be reported in accordance with the Section "9.6.2 Action When a Serious Adverse Event Occurs."

6.14 Efficacy Events

If the following efficacy events occur between randomization and the examination at completion of study treatment or the examination at discontinuation,†††† a survey will be performed according to "9.4 Adverse Event Information to Be Reported" and a survey of information such as the event classification, details of the event classification, and, depending on the situation in which the event occurred, cerebrovascular events (including intracranial bleeding), SEEs, cardiac ischemic events, and bleeding events, will be performed, and the information will be entered on the case report form. Copies of findings such as head imaging scans and ECGs that form the evidence for the diagnosis of the efficacy event will be submitted to the Sponsor. If the efficacy event that occurred is a stroke, it will be assessed using the modified Rankin Scale at (approximately) 1 month following stroke onset, and the assessment will be entered on the case report form.

- Stroke

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††††: For subjects withdrawn from study participation

- SEE
- MI
- TIA
- Hospitalization due to cardiovascular disease (CV) condition (including hospitalizations for bleeding)
- All-cause mortality (death due to CV and mortality due to all other causes)
- Venous thromboembolic event (VTE) (pulmonary thromboembolism [PTE] and deep vein thrombosis [DVT])

During study drug interruption and after study drug discontinuation, a survey of the above will be performed at least every 8 weeks, and the information will be entered on the case report form.
If the subject who developed the efficacy event is hospitalized at, or making visits to, another medical institution, the investigator or subinvestigator will contact the subject's physician at the medical institution where the subject is hospitalized or making visits, and make every attempt to obtain detailed information, as far as possible.

6.15 Bleeding Events

If a bleeding event (see 9.1 Bleeding Events) occurs between the initiation of study treatment and the examination at completion of study treatment or the examination at discontinuation,‡‡‡‡ a survey will be performed according to "9.4 Adverse Event Information to Be Reported" and a survey of information such as the event classification, details of the event classification, and depending on the situation in which the event occurred, laboratory tests, whether blood transfusion was performed, and the amount of blood transfused, will be performed, and the information will be entered on the case report form. In response to requests from the Clinical Bleeding Event Committee or the Sponsor, the investigator or subinvestigator will provide information such as imaging scan results that form the evidence for the diagnosis.
During study drug interruption and after study drug discontinuation, a survey of the above will be performed at least every 8 weeks, and the information will be entered on the case report form.
If the subject who developed the bleeding event is hospitalized at, or making visits to, another medical institution, the investigator or subinvestigator will contact the subject's physician at the medical institution where the subject is hospitalized or making visits, and

‡‡‡‡ For subjects withdrawn from study participation

make every attempt to obtain detailed information, as far as possible.

6.16 Long-term Storage of Clinical Specimens for Genomic and Genetic Analysis

Long-term storage (banking) of DNA specimens extracted from the subjects' blood by the following procedure will be performed, in preparation for the future case where new genomic or genetic information relating to the response to DU-176b (pharmacokinetic [PK] or PD) is obtained, or a serious adverse drug reaction is observed in a clinical study and genomic and genetic analysis is performed to discover the cause. A new research plan will be specified when the specific details of genomic and genetic analysis have been finalized.

Details of the handling of specimens are shown separately in the Procedures for the Handling and Transportation of Banking Specimens.

6.16.1 Targeted Specimens

At study sites where banking is approved, an explanation of banking will be given, and specimens will be sampled from subjects who provide informed consent (in-person consent only). The investigator or subinvestigator will enter the dates of informed consent on the case report forms of subjects who provide informed consent for banking. The investigator or subinvestigator will enter any information such as medical history (for example, allogeneic bone marrow transplantation) that may affect genomic or genetic information on the case report forms.

6.16.2 Sampling of Banking Specimens (Blood Sampling)

At any visit during the study treatment period from Visit 2 onwards, 7 mL of venous blood will be sampled from a cutaneous vein in the forearm of each subject. The sampled blood will be stored frozen as whole blood until the specimens are collected (at a temperature setting of −20°C or lower). The investigator or subinvestigator will enter the date of blood sampling on the case report form. So that the subjects' personal information is not leaked to external parties, the specimens will be managed by labeling them with codes that are unrelated to the subjects.

6.16.3 Duration of Storage

The duration of storage of banking specimens will be a maximum of 20 years from the day when notification of this study protocol is submitted.

6.16.4 Disclosure of the Results of Genomic and Genetic Analysis Using Banking Specimens

At present, the time when pharmacogenomics investigation using banking specimens will be performed, the method of genomic and genetic analysis, and whether or not the disclosure will be required, have not been determined. Accordingly, we do not plan to disclose the results of genomic and genetic analysis to parties such as the investigators or to subjects.

6.16.5 Disposal of Banking Specimens

After the end of the duration of storage, or if the subject withdraws consent during the storage period, banking specimens will promptly be disposed of. However, if genetic analysis has been performed before the end of the duration of storage or before the subject withdraws consent, the data related to these will not be discarded.

7. EFFICACY ENDPOINTS

The following efficacy events observed from randomization up to the examination at completion of study treatment or the examination at discontinuation[§§§§] will be assessed. Efficacy events will be reassessed by a Clinical Efficacy Event Committee independent of the assessment of the investigator or subinvestigator, and the assessment of the Clinical Efficacy Event Committee will be taken as the final assessment.

7.1 Primary Endpoint

For the composite endpoint of stroke and SEE observed from randomization up to the examination at completion of study treatment or the examination at discontinuation,[§§§§] the time to onset of the initial event will be assessed.

A stroke is defined as an abrupt onset, over minutes to hours, of focal neurological deficit symptoms that are generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit symptoms must either last more than 24 hours or result in death within 24 hours of symptom onset.

A SEE is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation).

Detailed definitions of stroke and SEE are shown separately in the Procedures for the

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[§§§§]: For subjects withdrawn from study participation

Clinical Efficacy Event Committee.

<Rationale and Suitability of Endpoint>
As this is a clinical study to confirm the effect of anticoagulants in preventing cerebroembolic stroke in patients with NVAF, we selected the standard endpoint used for efficacy assessment.

7.2 Secondary Endpoints

For the following endpoints, the time to onset of the initial event observed from randomization up to the examination at completion of study treatment or the examination at discontinuation***** will be assessed. Detailed definitions of individual events are shown separately in the Procedures for the Clinical Efficacy Event Committee and the Procedures for the Clinical Bleeding Event Committee.

1) Composite of stroke, SEE, and death due to CV
2) Major adverse cardiovascular events (MACE): non-fatal MI, non-fatal stroke, non-fatal SEE, or deaths due to CV or bleeding
3) Stroke, SEE, and all-cause mortality
4) Net clinical benefit: stroke, SEE, major bleeding, and all-cause mortality
5) All-cause mortality

7.3 Other Endpoints

The following endpoints will be used.

1) Hospitalization due to CV condition (including hospitalizations for bleeding)
2) Modified Rankin Scale (approximately) 1 month after the onset of stroke
3) Stroke, SEE, and TIA
4) Number of occurrences of stroke and SEE
5) VTE (PTE and DVT)

8. PHARMACOKINETIC ENDPOINTS

The plasma DU-176 concentration at Week 8 (Visit 3) during the study treatment period will be assessed.

9. SAFETY ENDPOINTS

The following items observed between the initiation of study treatment and the

*****: For subjects withdrawn from study participation

examination at completion of study treatment or the examination at discontinuation†††††
will be assessed.

1) Major bleeding
2) Major bleeding and clinically relevant non-major bleeding
3) Clinically relevant non-major bleeding
4) Minor bleeding
5) All bleeding events (composite of major bleeding, clinically relevant non-major bleeding, and minor bleeding)
6) Adverse events
7) Adverse drug reactions

9.1 Bleeding Events

Bleeding-related adverse events observed between the initiation of study treatment and the examination at completion of study treatment or the examination at discontinuation††††† will be assessed as bleeding events. Bleeding events will be reassessed by a Clinical Bleeding Event Committee independent of the assessment of the investigator or subinvestigator, and the assessment of the Clinical Bleeding Event Committee will be taken as the final assessment.
Bleeding events will be classified into major bleeding, clinically relevant non-major bleeding, and minor bleeding according to the following definitions. Detailed definitions of bleeding events are shown separately in "Procedures for the Clinical Bleeding Event Committee."

9.1.1 Major Bleeding

Overt bleeding that meets at least 1 of the following criteria will be taken to be major bleeding.

- Fatal bleeding
- Retroperitoneal, intracranial, intraocular, intrathecal, intraarticular, or periarticular bleeding, or symptomatic intramuscular bleeding accompanied by compartment syndrome
- Clinically overt bleeding that decreases hemoglobin by at least 2.0 g/dL and requires blood transfusion*

  *: Transfusion of 1 unit of red cell concentrates or whole blood (about 200 mL) will be converted to a decrease in hemoglobin of 1.0 g/dL. For bleeding related to a surgical

†††††: For subjects withdrawn from study participation

procedure, bleeding in excess of the usual quantity of bleeding for the surgery or procedure will be considered. If there are no data for hemoglobin, the criterion will be bleeding that decreases the hematocrit level by at least 6.0% and requires blood transfusion.

9.1.2 Clinically Relevant Non-major Bleeding

Clinically overt bleeding that requires treatment will be taken to be clinically relevant non-major bleeding. For example, this includes (but is not limited to) the following diagnostic tests and treatment. The definition of "requiring treatment" does not include outpatient examinations that do not involve the following medical procedures (diagnostic tests or treatment), or procedures similar to these. Clinically relevant non-major bleeding must be visually confirmed by tests or radiological imaging.

- Hospitalization or prolongation of existing hospitalization
- Laboratory tests
- Imaging tests
- Endoscopic tests, Colonoscopy tests, cystoscopy tests, bronchoscopy tests
- Nasal cavity packing
- Pressure hemostasis
- Ultrasound-guided compression for aneurysm
- Coil embolization
- Cardioactive therapy
- Surgery
- Interruption or discontinuation of the study drug at the instruction of a physician
- Change in concomitant therapy at the instruction of a physician (such as dose reduction or discontinuation of aspirin)

9.1.3 Minor Bleeding

Other overt bleeding events that do not meet the criteria for major bleeding or clinically relevant non-major bleeding will be taken to be minor bleeding (for example, epistaxis that does not require treatment).

All events other than the above (such as a decrease in hemoglobin without overt bleeding) will all be classified as "no bleeding event."

9.2 Definition of Adverse Events

An adverse event is any unfavorable or unintended sign (including abnormal laboratory findings or vital signs), symptom or disease by the examination at completion of study treatment (the final follow-up examination for subjects who continue the study treatment)

or the examination at discontinuation,‡‡‡‡‡ and which does not necessarily have to have a causal relationship to this study drug.

Symptoms or diseases occurring before the study treatment will be entered on case report forms as concurrent conditions, and will not be considered adverse events. However, if a concurrent condition becomes aggravated during the study treatment, it will be handled as an adverse event, and the day on which aggravation was found will be considered to be the onset date of the adverse event.

9.3 Definition of Serious Adverse Events

Serious adverse events are adverse events that meet any of the following criteria.

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Disability
- Risk of disability
- Serious equivalent to the above
- Resulting in congenital disease or anomaly in the next generation

9.4 Adverse Event Information to Be Reported

If an adverse event occurs during the period from the initiation of study treatment to the examination at completion of study treatment, the items shown in Table 9-1 will be surveyed and entered on documents such as the case report form. When symptoms are surveyed by medical interview, the question “Have you had any symptoms that concern you between your last visit and this visit?” will be asked, to elicit free responses from subjects. Medical interviews or question sheets about specific symptoms will not be used to check for adverse events.

‡‡‡‡‡: For subjects withdrawn from study participation

Table 9-1 Information to Be Reported When an Adverse Event Occurs

Item of Information		Details to Report	
Details of adverse event		Adverse event term and onset date	
Action taken for adverse event		Details of study drug action taken and other action taken	
Outcome		Outcome type, day of outcome assessment, and date of resolution	
	Outcome type	Recovered/ resolved	The adverse event has been resolved and the subject has recovered to the state before the adverse event occurred
		Recovering/ resolving	The adverse event has been almost resolved and the subject has nearly recovered to the state before the adverse event occurred
		Not recovered/ not resolved	The adverse event has not been resolved, and the subject is in a state similar to that when the adverse event occurred (unchanged)
		Recovered/ resolved with sequelae/residual effect(s) present	The adverse event has been resolved, but the subject has sequelae
		Fatal	This indicates that the investigators consider that the adverse event is related to the death, or that a relationship cannot be ruled out, and does not apply in cases where the death is due to a cause such as aggravation of the disease under study
		Unknown	There is no information and the outcome is unknown
Severity		Mild	Does not interfere with subject's usual function, and is easily tolerated
		Moderate	Enough to cause interference with usual activity
		Severe	Enough to cause inability to do usual activity
Seriousness		Serious/nonserious	
Causal relationship		Relationship classification (based on the following relationship classification), reason for causal relationship assessment	
	Relationship classification	Related	The onset of the adverse event follows a reasonable temporal sequence from study treatment, and cannot be reasonably considered to be due to the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications), and a relationship with the study drug cannot be ruled out The onset of the adverse event follows a reasonable temporal sequence from study treatment, and is a known reaction to the drug under study or its chemical group, or can be explained by known pharmacology
		Not related	The onset of the adverse event does not follow a reasonable temporal sequence from study treatment, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications), and a relationship with the study drug can be ruled out

9.5 Definition of Adverse Drug Reactions

Adverse events for which the relationship with the study drug is considered to be "related" will be treated as adverse drug reactions.

9.6 Action When an Adverse Event Occurs

9.6.1 Action When an Adverse Event Occurs

If an adverse event occurs, the investigator or subinvestigator will take suitable action, and report to the Sponsor if necessary, and, as far as possible, observe the subject's course (even after the end of the specified observation period) until the adverse event is resolved to the state before onset or is resolving. However, even if the adverse event is not resolved and is not resolving, observation will be ended in the study, after an explanation is provided to the subject (or legally acceptable representative) if it can be considered that the subject's condition is stable and the subject's safety is ensured (however, treatment for the relevant symptoms will continue).

9.6.2 Action When a Serious Adverse Event Occurs

If a serious adverse event occurs, the investigator or subinvestigator will take suitable action, and will promptly report the details of the event to the Sponsor by telephone or fax. The investigator will promptly report these details in writing to the Sponsor and the director of the study site. The written report to the director of the study site will follow the procedure and format for the study site. This action will be taken until the final follow-up examination.

10. OTHER ENDPOINTS

10.1 Pharmacodynamics (Pharmacodynamic Indicators and Biomarkers)

At Week 8 of the study treatment period (Visit 3), PD indicators (PT and aPTT) and biomarkers (D-dimer and F1+2) will be assessed.

11. STATISTICAL ANALYSES

This is an overview of the statistical analysis. A more detailed description of analytical methods will be specified in the Statistical Analysis Plan.

11.1 Objective of Analysis

To evaluate the superiority of 15 mg of DU-176b compared to placebo, with regard to the

composite primary efficacy endpoint of stroke and SEE.

11.2 Analysis Sets

After case report forms have been locked, and before unblinding, the Sponsor will decide on the handling each subject, after discussion with the medical experts if necessary. After receiving advice from the medical experts, the Sponsor will decide on the handling of subjects not specified in the protocol.
The major efficacy analysis set will be the intent-to-treat (ITT) set, but analysis of the modified intent-to-treat (mITT) set and per protocol set (PPS) will also be conducted as sensitivity analysis.

11.2.1 Efficacy Analysis Sets

11.2.1.1 Intent-to-treat Set

This set will include all randomized subjects, whether or not they receive a single dose of the study drug. Analyses will be based on the randomized treatment even if a subject inadvertently receives the incorrect drug or dosage. The reference date for consideration of endpoints is the randomization date (the times to onset of events will be calculated starting from the randomization date).

11.2.1.2 Modified Intent-to-treat Set

This set will include all randomized subjects who receive at least one tablet of the study drug. Analyses will be based on the randomized treatment even if a subject inadvertently receives the incorrect drug or dosage. The reference date for consideration of endpoints is the initial dose of study drug date (the times to onset of events will be calculated starting from the initial dose of study drug date).

11.2.1.3 Per Protocol Set

This set will include all randomized subjects who receive at least one tablet of the study drug and do not have any major protocol violations (as defined prior to unblinding of the database for final analyses). Analyses will be based on the randomized treatment even if a subject inadvertently receives the incorrect drug or dosage. The reference date for consideration of endpoints is the initial dose of study drug date (the times to onset of events will be calculated starting from the initial dose of study drug date).

11.2.2 Pharmacokinetic Analysis Set

The PK analysis set will include all randomized subjects who meet the following criteria.

1) Subjects in the DU-176b group.
2) Subjects with no major protocol violations affecting PK.
3) Subjects with at least one usable plasma DU-176 concentration measurement.
4) Subjects with usable information on administration.

11.2.3 Pharmacodynamic Analysis Set

The PD (PD indicator and biomarker) analysis set will include all randomized subjects who meet the following criteria.

1) Subjects with no major protocol violations affecting PD.
2) Subjects with at least one usable PD indicator or biomarker measurement.

11.2.4 Safety Analysis Set

This set will include all randomized subjects who receive at least one tablet of the study drug. Analyses will be based on the randomized treatment, unless a subject inadvertently receives the incorrect drug or dosage during the entire study, in which case, the subject will be grouped according to the treatment actually received. The reference date for consideration of endpoints is the initial dose of study drug date (the times to onset of events will be calculated starting from the initial dose of study drug date).

11.3 Handling of Data

Before unblinding, the Sponsor will decide on the handling of data after discussion with the medical experts, based on the criteria for the handling of data in this section, and then lock the data.

11.3.1 Handling of Protocol Deviation Data

Before the database is locked, the Sponsor will confirm with the expert about the cases to be analyzed and the criteria for handing the data for analysis, and will discuss and decide on the handling of problems not specified at the planning stage, and prepare records of these decisions.

11.3.2 Handling of Survey and Measurement Times

The eligibility assessment period will be within the 30 days after the day of informed consent, which will be counted as Day 0. The window for surveys and measurements

for each visit will be within 14 days before or after the specified date, which will be considered Day 0. The window for the examination at completion of study treatment will be 60 days after the date of declaration of completion of the study, which will be considered Day 0. The window for the examination at discontinuation will be 7 days after the day of discontinuation, which will be considered Day 0. The window for the final follow-up will be 30 to 37 days after the day of the examination at completion of study treatment, which will be considered Day 0 (For subjects who continue the study treatment after the completion of study treatment, in principle, within a month from the day of notifying their study treatment assignments as Day 0.). If multiple measurements are made within the window, the measurements made on the day nearest to the specified day of measurement will be selected. If there are measurements before and after the specified day that are the same number of days away, the latter measurements will be selected.

Data that do not meet the handling criteria will be excluded from analysis. If there are no data that meet the handling criteria, the relevant data point will be handled as being missing.

11.3.3 Handling of Missing Data

No missing data will be imputed with estimated or calculated values.

11.4 Statistical Analysis Items and Analysis Methods

11.4.1 Baseline Subject Characteristics

Distributions and summary statistics will be calculated by treatment group for baseline subject characteristics (demographic and reference ranges).

11.4.2 Efficacy Analysis

11.4.2.1 Primary Endpoint

11.4.2.1.1 Primary Analysis

For the composite endpoint of stroke and SEE observed from randomization up to the examination at completion of study treatment or the examination at discontinuation,§§§§§ the time to onset of the initial event* will be compared. The treatment group will be compared based on a Cox proportional hazard model with the $CHADS_2$ score (≤ 2 or ≥ 3) as covariate (significance level 5%, 2-sided, confidence coefficient for estimates: 95%). If any factors affecting the primary endpoint are found in a blinded review before data are

§§§§§: For subjects withdrawn from study participation

locked, these factors will also be considered as covariates.

*: This will apply to all events whether or not the subject receives the study drug. The time to onset of the initial event is defined as the time from the day of randomization to the initial event experienced by a subject. For subjects who do not experience an event during the study, the time to onset of the initial event will be censored at the day of the examination at completion of study treatment, the day of the examination at discontinuation (for subjects withdrawn from study participation) or death, whichever comes first.

11.4.2.1.2 Secondary Analysis

The cumulative incidence of events will be estimated for each treatment group using the Kaplan-Meier method. Sensitivity analysis of the events that occur during the "on-treatment" period** in the mITT analysis set and PPS will be performed.

**: "On-treatment" period is defined as the study treatment period and up to 3 days after the last dose (approximately five times the half-life [$T_{1/2}$] of DU-176 corresponds to 3 days). If the subject resumes study drug, the subject is considered at risk again. However, in analysis, a subject who has received the study drug up to the examination at completion of study treatment will not be considered at risk after the day of the examination at completion of study treatment, and events that occur on or after the day of the examination at completion of study treatment will not be included in analysis. For subjects who do not experience an event while at risk, the time to onset of the initial event will be censored at 3 days after the final dose, the day of the examination at completion of study treatment, the examination at discontinuation (for subjects withdrawn from study participation), the day of the subject's last assessment, or death, whichever comes first.

11.4.2.2 Secondary Endpoints

The following secondary endpoints will be analyzed in the same way as primary endpoints.

1) Composite of stroke, SEE, and death due to CV
2) MACE
3) Stroke, SEE, and all-cause mortality
4) Net clinical benefit: stroke, SEE, major bleeding, and all-cause mortality
5) All-cause mortality

11.4.2.3 Other Endpoints

The following other endpoints will be descriptively summarized.

1) Hospitalization due to CV condition (including hospitalizations for bleeding)
2) Modified Rankin Scale (approximately) 1 month after the onset of stroke
3) Stroke, SEE, and TIA
4) Number of occurrences of stroke and SEE
5) VTE (PTE and DVT)

11.4.2.4 Other Analysis Methods

Subgroup analysis using the major baseline subject characteristics (demographic and reference ranges) will be conducted for the primary endpoint. Details of subgroups will be specified in the Statistical Analysis Plan.

11.4.3 Pharmacokinetic Analysis

Summary statistics for plasma DU-176 concentration will be calculated at each blood sampling point, and a plot of the time course will be prepared.

11.4.4 Pharmacodynamic Analysis

Summary statistics for PD indicators (PT and aPTT) and biomarkers (D-dimer and F1+2) will be calculated at each blood sampling point, and the changes before and after administration (time course) will be plotted.

11.4.5 Safety Analysis

Unless otherwise stated, the safety analysis set will be used for safety analysis. The analysis period will be from the initiation of study treatment to the examination at completion of study treatment or the examination at discontinuation******. Serious adverse events observed during the period from the examination at completion of study treatment to the final follow-up examination and data obtained at the final follow-up examination will be tabulated separately, as necessary. Adverse events will be coded using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA), and system organ classes will be tabulated using MedDRA System Organ Classes, and adverse event terms will be tabulated using Preferred Terms.

11.4.5.1 Bleeding Events

Bleeding events will be classified into the following categories and summarized by treatment group, and analyzed in the same way as the primary endpoint.

1) Major bleeding
2) Major bleeding and clinically relevant non-major bleeding
3) Clinically relevant non-major bleeding
4) Minor bleeding

****** Subjects withdrawn from study participation

5) All bleeding events

11.4.5.2 Adverse Events

Incidences of adverse events will be calculated by treatment group. Frequencies of adverse events will also be tabulated by event and by severity. Adverse drug reactions will be analyzed in the same way.

In tabulation by System Organ Class or Preferred Term, if multiple adverse events with the same System Organ Class or Preferred Term occur in the same subject, these will be counted as a single event. System Organ Classes will be displayed in the internationally agreed order, and Preferred Terms will be displayed in code order. In this study, adverse events that occur after the initiation of study treatment (treatment emergent adverse events [TEAEs]) will be tabulated.

11.4.5.3 Laboratory Data

Summary statistics for hematology and blood chemistry tests will be calculated by time point and by treatment group, and changes (time courses) before and after administration will be plotted. A shift table of assessment on normal and abnormal values will also be prepared. Frequencies of measured indicators from urinalysis (except for urinary sediment) will also be tabulated by time point and by treatment group.

11.4.5.4 Vital Signs (Body Weight, Blood Pressure, and Pulse Rate)

Summary statistics for blood pressure (systolic and diastolic), pulse rate, and body weight will be calculated by time point and by treatment group, and changes (time courses) before and after administration of the study drug will be plotted.

11.4.5.5 Electrocardiograms

A frequency table by time point and by treatment group for the results of the physician's assessment of standard 12-lead ECGs will be prepared.

11.4.6 Blinded Review

Before the database is locked, a blinded review will be conducted. Details of the blinded review are specified in the blinded review plan. If it becomes necessary to make any changes to the analysis plan in the blinded review, changes will be made according to the procedure in "11.5 Changes to the Analysis Plan."

11.5 Changes to the Analysis Plan

If any changes are to be made to the method for handling data, or any changes are to be made to the analysis plan, for example in order to perform conversion of variables, the Sponsor will first consider whether these changes are appropriate, and the effect of the changes on the assessment of this study, before deciding whether the changes can be made. The Sponsor will record information including the contents of the discussion, whether changes were made, and the reasons for this, in written form, and will store this information. If changes are made, the details of the changes and the reasons for them will be documented in the clinical study report. Changes to the primary analysis listed in the protocol will be made in accordance with "15.7 Protocol Amendment."

11.5.1 Safety Data Monitoring Committee

The Sponsor will establish and run a safety data monitoring committee as a third party independent of the Sponsor, the investigator, and the coordinating committee.
The safety data monitoring committee will monitor safety data as necessary, and will consider matters such as whether it is possible to continue the study and whether it is necessary to change the protocol, and will make recommendations to the Sponsor.
Details are specified in the Procedure for the Safety Data Monitoring Committee.

11.6 Planned Sample Size

Four hundred subjects in each group, for a total of 800 subjects

<Rationale>
In this study, 65 primary endpoint events observed in the ITT analysis set between randomization and the examination at completion of study treatment will be collected. Under the conditions that the annual incidence in the placebo group is 5%/year, the hazard ratio of DU-176b relative to the placebo group is 0.5, the significance level is 5%, 2-tailed, and the power is 80%, the number of events required to evaluate the superiority is 65. Assuming that the duration of the subject enrollment period is 2 years and the duration of the follow-up period is 1.5 years, it is estimated that approximately 400 subjects will be enrolled in each group. Thus, the planned sample size will be a total of 800 subjects. This study is an event-driven study, and the total number of subjects may change as necessary depending on the number of target events collected.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will assure that the conduct of the study and the preparation of data, records, and reports, are in compliance with the following items by employing quality assurance and quality control systems based on the standard operating procedures specified by the Sponsor.

1) The protocol
2) The standards specified in Article 14 Paragraph 3 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (the Pharmaceutical and Medical Device Act).
3) The GCP Ministerial Ordinance

To assure the reliability and accuracy of all data relating to the study, the Sponsor will conduct quality control on the handling of data at each stage. The methods for quality control will be prepared in advance in accordance with the standard operating procedures specified by the Sponsor, and records of conducting quality control will be kept.
The Sponsor's responsible auditor will conduct a GCP audit as part of quality assurance activities, to assess whether this study is in compliance with GCP, the protocol, procedures, and the like, independent of and separate from usual monitoring and study quality control work.

13. FINANCING FOR PARTICIPATION, COMPENSATION FOR STUDY-RELATED INJURIES, AND INSURANCE

13.1 Financing for Participation

Payments such as those to relieve financial burden will be made to subjects according to the rules specified separately by the study site. This financing will be funded from the amounts paid by the Sponsor to the study site.

13.2 Compensation for Study-related Injuries

If the subject develops any study-related injuries, the investigator or subinvestigator will provide treatment and take other necessary measures. If the subject (or legally acceptable representative) requests a response to study-related injuries, the investigator or subinvestigator will promptly contact the Sponsor. The Sponsor will specify a procedure for providing compensation to the subject for study-related injuries, and take measures such as taking out insurance. The Sponsor will bear the proportion of costs

required to treat study-related injuries that would be borne by the subject, excluding the amount paid from sources such as health insurance. If the Sponsor has responsibility for compensation for sequelae, disabilities, or the like, the Sponsor will provide compensation commensurate with payments under the Adverse Drug Reaction Relief System. However, compensation will not necessary be provided in the case of the following injuries.

1) Injuries proved to have an obvious relationship with another cause
2) Injuries for which there is no reasonable temporal relationship between the study treatment and the injury
3) Injuries for which there is obviously a party at fault, such as road traffic accidents
4) Injuries due to a lack of therapeutic benefit, due to treatment being ineffective or due to administration of placebo
5) Injuries due to the subject or the subject's partner becoming pregnant during the study period
6) Injuries due to the subject failing to comply with the protocol without a proper reason

If the study-related injury is determined to be due to the deliberate fault or gross negligence of the study site or the subject, the subject may not be eligible for compensation, or the amount of compensation may be reduced.

13.3 Insurance

The Sponsor will take out the insurance necessary to provide compensation for study-related injuries. The study site will take out insurance and take other necessary measures in readiness for the occurrence of medical errors.

14. PUBLICATION POLICY

[redacted]

[redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1 Ethics

15.1.1 Ethical Conduct of the Study

This study will be conducted in compliance with the standards specified in the Pharmaceutical and Medical Device Act, Article 14, Paragraph 3, and Article 80-2 and Ministry of Health and Welfare Ordinance 28 dated 27 Mar 1997, the "Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs" (the GCP Ordinance). The conduct of the study will be in compliance with the ethical principles that have their origin in the Declaration of Helsinki, and the human rights, well-being, and safety of subjects will be protected to the maximum extent possible.

In addition to the above, banking of clinical specimens for genomic and genetic analysis and research using these specimens will be conducted in accordance with the "Ethical Guidelines for Human Genome/Gene Analysis Research"[27] and "Ethical Guidelines for Medical and Health Research Involving Human Subjects"[28] (only at study sites where genomic and genetic analysis or banking is approved).

15.1.2 Institutional Review Board

This study will be reviewed and approved by the Institutional Review Board (IRB) as specified in the GCP Ordinance Article 27 before being conducted. During the conduct of this study, once per year, or more frequently if requested by the IRB, the study will be reviewed to determine whether it can continue. In addition, if information that may affect the safety of subjects or the conduct of the study is obtained, the study will be reviewed to determine whether it can continue.

15.2 Subject Confidentiality

To protect the confidentiality of individual subjects, documents submitted from the study site to an external party will use subject identification codes to identify subjects, and identifying information about subjects such as names or medical record numbers will not be used. Persons who may learn confidential information about subjects (or legally

acceptable representatives) in the course of their work will maintain the confidentiality of this information.

15.3 Informed Consent

Before performing the examinations specified in the protocol for this study, the investigator or subinvestigator will explain the following information to the subject (and also to the legally acceptable representative, if the legally acceptable representative will provide consent) in an easily understandable way using the informed consent form, and obtain the subject's written informed consent to participate in the study, given of the subject's own free will. When obtaining informed consent, the investigator or subinvestigator will give the subject (or legally acceptable representative) ample time to decide whether or not to participate in the study, and will provide an opportunity to ask questions, and will provide thorough responses to these questions. As the subjects of this study will be patients with NVAF aged 80 years or older, more than a few of the patients will have dementia as a concurrent condition, and therefore, if the investigator or subinvestigator considers that it is not feasible to obtain written consent from the subject in person due to deterioration of cognitive function, the investigator or subinvestigator will also explain the study to a legally acceptable representative and obtain written consent, given of the legally acceptable representative's own free will. A legally acceptable representative is a person who is authorized to provide consent on behalf of a subject, and will be the subject's spouse, guardian, other caregiver, or other similar person, who is likely to act in the best interests of the subject, given the living circumstances and emotional relationship of the two people.

The investigator or subinvestigator who provided the explanation and the subject (or the legally acceptable representative, if the legally acceptable representative provided consent) will affix their names and seals to, or sign the informed consent form, and each will also enter the date. If a legally acceptable representative provided consent, the relationship with the subject will be stated on the consent form. If a supplementary explanation was provided to the subject (or legally acceptable representative) by study staff designated by the director of the study site, the member of the study staff will also affix his/her name and seals to, or sign the consent form, and enter the date, in addition to the investigator or subinvestigator. A copy of the consent form and written information will be provided to the subject (or legally acceptable representative), and the original consent form will be stored at the study site. The investigator or subinvestigator will record the fact that a copy of the consent form and written information have been

provided to the subject (or legally acceptable representative) on a document (such as the original consent form or medical records).
In addition, the investigator or subinvestigator will obtain written voluntary consent, separately from informed consent at the start of this study, from the subject (or the legally acceptable representative, if the legally acceptable representative provides consent) who is found to be necessary to continue the study treatment until the final follow-up examination at the time of the examination at completion of study treatment.

[Items to be explained to the subject (or legally acceptable representative)]

1) That the study involves research
2) The objective of the study
3) The study methodology (including the experimental aspects of the study, the inclusion criteria for subjects, and, if randomization will be performed, the probability of being assigned to each treatment)
4) The planned duration of subject's participation in the study
5) The planned number of subjects who will participate in the study
6) The expected benefits to the subject's mental and physical health from the study drug (or that no benefits are expected, if this is the case) and the expected disadvantages to the subject
7) Whether there are any alternative treatments, and their important potential benefits and risks
8) The compensation and treatment available to the subject in the event of study-related injuries
9) That the subject's participation in the study is voluntary, that the subject or the subject's legally acceptable representative may refuse to participate in the study or withdraw consent at any time, without penalty or loss of benefits to which the subject is otherwise entitled
10) That the subject or the subject's legally acceptable representative will be informed in a timely manner if any information becomes available that may affect the subject's or legally acceptable representative's willingness to continue participation in the study
11) The circumstances or reasons under which the subject's participation in the study may be terminated
12) That the monitor, responsible auditor, IRB, and regulatory authority will be granted access to original medical records, without violating the confidentiality of the subject, and that by affixing the names and seals to, or signing the consent form, the subject

or the subject's legally acceptable representative is authorizing such access

13) That the subject's confidentiality will be protected even if the results of the study are published
14) The expenses to the subject, if any
15) The payments to the subject, if any
16) The investigator or subinvestigator's name, job title, and contact information
17) The office at the study site to make enquiries to or person to contact for further information regarding the study or the rights of subjects, and whom to contact in the event of study-related injury
18) The subject's responsibilities
19) The type of IRBs reviewing whether or not the study is acceptable, and the items reviewed by each IRB and other information relating to IRBs involved in the study

15.4 Informed Consent for Pharmacogenomics and Biomarker Research

If long-term storage (banking) of specimens for genomic and genetic analysis with no set timing is conducted, the investigator or subinvestigator will explain the following information to the subject in an easily understandable way, and obtain the subject's written informed consent, given of the subject's own free will, and separately from the consent for the study (consent obtained from a legally acceptable representative is invalid). This consent will be obtained before specimens are sampled.

1) The characteristics and nature of the genetic information
2) The objective of the research
3) The research methodology
4) The expected benefits to the subject's mental and physical health from the research, and the expected disadvantages to the subject
5) That the subject's participation in the investigation of pharmacogenomics is voluntary, that the subject may refuse to participate in the study or withdraw consent at any time, without penalty, and that the subject's participation in the study will not be affected if the subject does not participate in this research
6) How specimens and data will be handled if consent is withdrawn
7) The methods for handling specimens, the storage period of specimens, and information relating to disposal of specimens
8) Compensation available to the subject
9) The disclosure and ownership of the results of research
10) The expenses to the subject, if any

11) That specimens will be provided free of charge by the subject
12) That the subject's confidentiality and other human rights will be protected

15.5 Provision of New Information Affecting the Conduct of the Study

If information is obtained that may affect the subject's (or legally acceptable representative's) willingness to continue participation in the study, the investigator or subinvestigator will promptly explain the relevant information to the subject (or legally acceptable representative) and confirm the subject's (or legally acceptable representative's) willingness to continue participation in the study. The investigator or subinvestigator will record on a document such as medical records the date of explanation, the person providing the explanation, the contents of the explanation, the willingness of the subject (or legally acceptable representative), and the date of confirmation. If necessary, the investigator will also promptly amend the informed consent form and submit it to the Sponsor and report it to the director of the study site and receive approval from the IRB. If there are any subjects already participating in the study, the informed consent of the subjects (or legally acceptable representatives) will be obtained again in the same way as above using the amended informed consent form, and the subjects (or legally acceptable representatives) will be provided with copies of the consent form and written information. The investigator or subinvestigator will record the fact that a copy of the consent form and written information have been provided to the subject (or legally acceptable representative) on a document (such as the original consent form or medical records).

15.6 Planned Study Duration

24 May 2016 to 30 Sep 2020

15.7 Protocol Amendment

If the protocol is amended after the start of the study, the Sponsor will, if necessary, discuss with the medical experts whether the changes are appropriate and the influence on the assessment of the study, and will then make a decision about the amendment. The Sponsor will make a clear written record of information including the contents of the discussion, whether an amendment was made, and the reason for this, and will store this record.

The Sponsor will promptly inform the investigator of the details of the protocol amendment. If the version number of the protocol is amended, the Sponsor will again

conclude a written agreement with the investigator and proceed with the process specified by the study site.

15.8 Termination or Interruption of the Study

15.8.1 Termination or Interruption of the Study

If any of the following criteria are met, and the Sponsor determines that it is not feasible to continue the study, the Sponsor will temporarily discontinue the whole or a part of the study. After this, the Sponsor will decide whether to terminate the whole or a part of the study and make a written record of this decision.

1) If new safety information relating to the study drug or information about serious adverse events is obtained
2) If there is a major breach of GCP or a major deviation from the protocol by either the Sponsor, study site, or investigator
3) If a recommendation to terminate the study is received from the Safety Data Monitoring Committee, for example due to a major safety problem (detailed standards are specified in the Procedure for the Safety Data Monitoring Committee)
4) If other new information is obtained during the conduct of the study

If, in discussion with parties such as the medical experts, the Sponsor decides to terminate a part or the whole of the study, or decides to terminate the whole study due to the recommendation of the Safety Data Monitoring Committee, the Sponsor will promptly provide written notice of this fact and the reason for it to the director of the study site. The director of the study site will promptly provide written notice of this fact and the reason for it to the investigator and the IRB.
Regardless of the reason, if the study is terminated or temporarily discontinued, the investigator will promptly notify subjects participating in the study (or legally acceptable representatives) of this fact, and will take suitable measures and perform tests or the like to confirm the safety of subjects.

15.8.2 Completion of the Study

Based on the incidence of events as this study progresses, the Sponsor will discuss with the medical experts about the time to perform the examination at completion of study treatment for the subjects.
When the Sponsor has decided on the time to perform the examination at completion of study treatment, the Sponsor will provide written notice of the fact and the reason for it to

the investigator and the director of the study site.
The investigator or subinvestigator will promptly notify subjects participating in the study (or legally acceptable representatives) of this fact, and will perform the examination at completion of study treatment within 60 days.

15.9 Procedures for Preparing the Case Report Form and Remarks

In this study, the following will be prepared: case report forms (prepared by the investigator), bleeding event assessment forms (prepared by the Clinical Bleeding Event Committee), efficacy event assessment forms (prepared by the Clinical Efficacy Event Committee), laboratory measurement reports (prepared by the central laboratory), drug concentration measurement reports (prepared by the central laboratory), PD indicator measurement reports (prepared by the central laboratory), and biomarker measurement reports (prepared by the central laboratory). The method for preparing assessment forms and measurement reports will be specified elsewhere.

15.9.1 Style of the Case Report Form

In this study, case report forms will be entered electronically using an electronic data collection system for preparing case report forms (EDC system, Table 15.9-1). Case report forms (including audit traces) will be prepared for each subject, and the case report forms signed by the investigator will be treated as originals. A validated EDC system will be used.

Table 15.9-1 The EDC System

Name of EDC system	Medidata Rave®
Company developing EDC system	Medidata Solutions, Inc.
Entry method	Web-based data entry
Entry terminals	Personal computers at the medical institution
Prohibited OSs	None
Browser	Medidata RAVE® supports browsers in compliance with HTML 5, and CSS 2. Browsers must also have JavaScript enabled.
Recommended screen resolution	1024 × 764 or higher
Recommended connection speed	128 kbps or higher
Other	Adobe Flash Player: ver. 10 or higher

15.9.2 Preparing Case Report Forms

The investigator will receive training in digital signatures before preparing case report forms, and the record of this will be used in place of a list of signatures and seal marks.

1) Case report forms will be prepared for all subjects from whom consent has been received, including cases where consent was provided by a legally acceptable representative.
2) The investigator or subinvestigator will prepare case report forms according to the Guide to Entering and Editing Case Report Forms provided by the Sponsor.
3) If the study staff assists in the preparation of a case report form, the study staff will follow the directions of the investigator or subinvestigator.
4) The investigator will submit the case report forms to the Sponsor and store copies of them.
5) If there are any contradictions between the data entered on the case report forms and the source documents, the investigator will separately prepare records explaining the reason for this and will submit them to the Sponsor, storing a copy.

15.9.3 Affixation of Name and Seal or Signature to Case Report Forms

The investigator will confirm the case report forms prepared at the study site and sign them electronically.

15.9.4 Changing or Editing the Contents Entered on Case Report Forms

1) The investigator, subinvestigator, or study staff will edit case report forms according to the Guide to Entering and Editing Case Report Forms provided by the Sponsor.
2) The investigator will have responsibility for the contents entered on case report forms, and will store copies of all records of them, including changes and edits.

15.10 Storage of Source Documents and Other Records

15.10.1 Definition of Source Documents

"Source documents" refers to the original documents or data and certified copies of them specified in ICH-GCP 1.52, and includes the records (source data) necessary for the reconstruction and evaluation of the course of the clinical study. For example, hospital records, clinical charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilms or magnetic media, X-ray photographs, subject files,

and records stored at pharmacies, laboratories, and the medical technology department involved in the clinical study.

15.10.2 Record Keeping

15.10.2.1 Institutional Review Board

The person who established the IRB will store the standard operating procedures, list of board members, submitted documents, minutes and summaries of meetings, and records such as letters until the later of the date 1) or 2) below. If the Sponsor requires records to be stored for a longer period, the person who established the IRB will discuss the duration of storage and the storage method with the Sponsor.

1) The date of approval relating to this study (or, if development is terminated, the date 3 years after the day when notification of termination of development is received from the Sponsor)
2) The date 3 years after the discontinuation or completion of the study

15.10.2.2 Study Site

The director of the study site or the person responsible for record keeping will store the documents or records relating to the clinical study that are to be stored at the study site until the later of the date 1) or 2) below. If the Sponsor requires records to be stored for a longer period, the director of the study site or the person responsible for record keeping will discuss the duration of storage and the storage method with the Sponsor. When records are stored, a person responsible for record keeping will be designated for each record.

The director of the study site or the person responsible for record keeping will take measures to ensure that these records are not lost or discarded during the period for which they are to be stored, and so that they can be presented in response to requests.

1) The date of approval of this Investigational Product (or, if development is terminated, the date 3 years after the day when notification of termination of development is received from the Sponsor)
2) The date 3 years after the discontinuation or completion of the study

In order to respond to the withdrawal of consent for long-term storage (banking) of specimens for genomic and genetic analysis by subjects after the completion of the study, the study site will store the subject screening list for up to 20 years after the completion of the study.

15.10.2.3 Sponsor

The Sponsor will store the documents or records relating to the clinical study that are to be stored until the later of the date 1) or 2) below.

1) The date 5 years after the day of approval relating to this study (or, if development is terminated, the date 3 years after the day when the decision to terminate development is made), or the date of completion of reexamination, whichever is later
2) The date 3 years after the discontinuation or completion of the study

15.11 Direct Access to Source Documents

When monitoring or auditing is conducted by the Sponsor or reviews are conducted by the regulatory authority or IRB, the director of the study site and investigator will provide direct access to all records relating to the study, including source documents. The Sponsor will conduct monitoring and auditing, and directly access records relating to the study, including source documents, at the study site, to confirm that the study is being conducted appropriately and that the reliability of data is thoroughly ensured. The Sponsor will hold prior discussions with the investigator about the method for direct access to source documents.

15.12 Organization

The organization for this study is as follows. Each assigned person will work in accordance with the Procedure for Assignment of the Study Organization at Daiichi Sankyo Co., Ltd.

15.12.1 Sponsor

Daiichi Sankyo Co., Ltd.
3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426

Vice president of clinical study department:
[redacted] Vice President, Clinical Development Department

Monitor (representative): [redacted] Clinical Study Leader, Clinical Development Department
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
[redacted]

Person responsible for study drug management:

[redacted] Clinical Supply Management Department

Person responsible for PK analysis:

[redacted] Clinical Pharmacology Department

Person responsible for concentration measurements:

[redacted] Biomarker Department

Sub-Functional Lead of Data Management:

[redacted] Biostatistics & Data Management Department

Sub-Functional Lead of Biostatistics:

[redacted] Biostatistics & Data Management Department

Person responsible for quality management:

[redacted] Development Function

Person responsible for safety information and strategy (strategy):

[redacted] Pharmacovigilance Department

Person responsible for safety information and strategy (assessment):

[redacted] Pharmacovigilance Department

Person responsible for genomic and genetic analysis:

[redacted] Biomarker Department

Person responsible for banking of genetic analysis specimens:

[redacted] Biomarker Department

Office for enquiries about banking of genetic analysis specimens:

Biomarker Department
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
[redacted]

15.12.2 Medical Experts

[redacted] The Cardiovascular Institute
3-2-19 Nishi-Azabu, Minato-ku, Tokyo 106-0031
[redacted]

[redacted] Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo

7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655
[redacted]

Role: To give advice on the planning and conduct of the study, and the preparation of the clinical study report, from a medical perspective, and to act as the person giving approval for the clinical study report, signing the clinical study report if it is determined to be suitable for approval.

15.12.3 Developing and Supporting the Interactive Response Technology System

PAREXEL Informatics, Patient Technology Solutions, IRT Services
Person responsible: [redacted]
9F RBM East Yaesu Building 2-9-1, Hatchobori, Chuo-ku, Tokyo 104-0032
[redacted]

Role: To manage, maintain and support the operation of the systems relating to subject enrollment and logistical management of the study drug, based on an outsourcing contract.

15.12.4 EDC System Development

Medidata Solutions, Inc.
Person responsible: [redacted]
350 Hudson Street, 9th Floor, New York, New York 10014, USA
[redacted]

Role: To manage and maintain operation of the EDC system, based on an outsourcing contract.

15.12.5 EDC System Support

Fujitsu Limited
Person responsible: [redacted]
Tokyu REIT Kamata Building, 5-13-2 Kamata, Ota-ku, Tokyo 108-0075
[redacted]

Role: To support the EDC system, based on an outsourcing contract.

15.12.6 Contract Research Organization

PAREXEL International Inc.
Persons responsible: [redacted] Clinical Operation Leaders, Clinical Development

Department
Kayabacho First Building, 1-17-21, Shinkawa, Chuo-ku, Tokyo 104-0033
[redacted]

Role: To perform monitoring activities according to the Sponsor's standard operating procedures, based on an outsourcing contract.

15.12.7 Study Sites and Investigators

The addresses and telephone numbers of the study sites and the names and job titles of the investigators are as shown in Attachment 1.

Role: Based on discussion with the Sponsor, to agree on the protocol, prepare and amend the informed consent form, select subjects and obtain consent, instruct and oversee the subinvestigators and study staff, provide documents and information, cooperate with monitoring and auditing, report deviations from or changes to the protocol, report adverse events, prepare case report forms, and store documents or records relating to the clinical study.

15.12.8 Coordinating Committee

Chair of Coordinating Committee:
[redacted], Advanced Arrhythmia Therapeutic Branch,
Division of Cardiology, Saiseikai Kumamoto Hospital
5-3-1 Chikami, Minami-ku, Kumamoto City, Kumamoto 861-4193
[redacted]

Coordinating Committee Members
[redacted] Tosei General Hospital
160 Nishioiwake-cho, Seto City, Aichi 489-8642
[redacted]

[redacted] Kyoto Medical Center, National Hospital Organization
1-1 Fukakusa Mukaihatacho, Fushimi-ku, Kyoto City, Kyoto 612-8555
[redacted]

[redacted] Osaka General Medical Center, Osaka Prefectural Hospital Organization

3-1-56 Bandai Higashi, Sumiyoshi-ku, Osaka City 558-8558
[redacted]

[redacted] Department of Cardiovascular Medicine, Graduate School of Nippon Medical School
1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603
[redacted]

[redacted] Department of Cardiology, Naha City Hospital
2-31-1 Furujima, Naha-shi, Okinawa 902-8511
[redacted]

Role: Has responsibility for coordinating with investigators at study sites to conduct the study. Conducts coordination when there are questions at study sites about the interpretation of details such as the method of conduct or assessment in the protocol.

15.12.9 Independent Biostatistician

PAREXEL Informatics
Person responsible: [redacted] Senior Statistical Design & Trial Supplies Consultant
Castle Wharf, 4 Canal Street, Nottingham, NG1 7EH, UK
[redacted]

Role: To prepare and manage the randomization schedule for assigning subjects based on the specifications in the protocol.

15.12.10 Central Laboratory

15.12.10.1 Drug Concentration Measurement

Q^2 Solutions
Person responsible: [redacted] Study Director Bioanalysis
19 Brown Road Ithaca, NY 14850, USA
[redacted]

Role: To measure and store specimens sent by SRL, Inc., based on a contract with the Sponsor.

15.12.10.2 Laboratory Measurements, Measurement of Pharmacodynamic Indicators and Collection and Measurement of Biomarker Specimens, and Collection of Specimens for Plasma Drug Concentration Measurement and Clinical Specimens for Genomic and Genetic Analysis

Contractor: SRL Medisearch Inc.
Person responsible: [redacted] Development Business Division
10F Shinjuku-I-Land Tower, 6-5-1 Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1310
[redacted]

Testing laboratory: SRL, Inc.
Person responsible: [redacted] Testing Division
2-1-1 Nishi Shinjuku, Shinjuku-ku, Tokyo 163-0409
[redacted]

Role: To collect, send, store, and measure specimens provided by study sites, based on a contract with the Sponsor.

15.12.10.3 Contractor for Storage and Management of Clinical Specimens for Genomic and Genetic Analysis

SRL Medisearch Inc.
Person responsible: [redacted] Clinical Study Support Department
10F, Shinjuku I-Land-Tower, 6-5-1 Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1310
[redacted]

Role: To perform tasks such as extracting DNA from clinical specimens (such as blood) for genomic and genetic analysis and managing the storage (banking) of specimens, and disposing of them

15.12.11 Clinical Efficacy Event Committee

[redacted] Kyushu University Faculty of Medical Sciences
3-1-1 Maidashi, Higashi-ku, Fukuoka City, Fukuoka 812-8582
[redacted]

[redacted] Center of Cardiovascular Disease, Kurume University Hospital
67 Asahimachi, Kurume City, Fukuoka 830-0011
[redacted]

Role: To make a final assessment on efficacy events according to a procedure specified separately, as committee members who are independent from the Sponsor, investigator, or coordinating investigators.

15.12.12 Clinical Bleeding Event Committee

[redacted] International University of Health and Welfare
Sanno Hospital, 8-10-16 Akasaka, Minato-ku, Tokyo 107-0052
[redacted]

[redacted] Tokyo Women's Medical University Hospital
8-1 Kawadacho, Shinjuku-ku, Tokyo 162-8666
[redacted]

Role: To make a final assessment on bleeding events according to a procedure specified separately, as committee members who are independent from the Sponsor, investigator, or coordinating investigators.

15.12.13 Safety Data Monitoring Committee

[redacted] Saiseikai Toyama Hospital
33-1 Kusunoki, Toyama City, Toyama 931-8533
[redacted]

[redacted] Osaka National Hospital, National Hospital Organization
2-1-14 Hoenzaka, Chuo-ku, Osaka City 540-0006
[redacted]

[redacted] Department of Cerebrovascular Medicine and Neurology, Kyushu Medical Center, National Hospital Organization
1-8-1 Jigyohama, Chuo-ku, Fukuoka City, Fukuoka 810-8563
[redacted]

[redacted] Biostatistics and Clinical Epidemiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences

2630 Sugitani, Toyama City 930-0194
[redacted]

Role: To monitor safety data as necessary, consider matters such as whether the clinical study can be continued and the need for changes to the study protocol, and make recommendations to the Sponsor, according to a procedure specified separately, with committee members who are independent from the Sponsor, investigator, or coordinating investigators.

15.12.14 Department Responsible for Audit

R&D & PV Quality Assurance Department, Quality & Safety Management Division, Daiichi Sankyo Co., Ltd.
Person responsible: [redacted]
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
[redacted]

Role: To perform GCP audits.

15.13 Emergency Contact Information

Daiichi Sankyo Emergency Center, 24 hours a day, 365 days a year
[redacted]

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ATTACHMENT

Attachment 1 List of Study Sites and Investigators

APPENDICES

Appendix 1 Falling Risk

Survey the following items and enter them on the case report form.

1. History of falling
2. Lower limb strength
3. Poor balance
4. Reduced cognitive function
5. Orthostatic hypotension
6. Use of psychotropic drugs
7. Severe arthritis
8. Dizziness

Appendix 2 Falling Score[23)]

Survey the following items and enter them on the case report form.

1. Has the subject fallen in the past year? (yes/no)
   If so, how many times? (times/year)
2. Does the subject sometimes trip or stumble? (yes/no)
3. Can the subject ascend or descend stairs without holding a handrail? (yes/no)
4. Has the subject's walking speed decreased? (yes/no)
5. Can the subject finish crossing the road at a pedestrian crossing while the signal is green? (yes/no)
6. Can the subject continue walking for about 1 kilometer without a break? (yes/no)
7. Can the subject stand on one leg for about 5 seconds? (yes/no)
8. Does the subject use a cane? (yes/no)
9. Can the subject wring out a towel? (yes/no)
10. Does the subject have dizziness or faintness? (yes/no)
11. Does the subject have a stooped or rounded back? (yes/no)
12. Does the subject have knee pain? (yes/no)
13. Does the subject have visual disturbance? (yes/no)
14. Does the subject have hearing disturbance? (yes/no)
15. Does the subject have forgetfulness that concerns him/her? (yes/no)
16. Is the subject anxious about the possibility of falling? (yes/no)
17. Does the subject receive 5 or more drugs every day? (yes/no)
18. Does the subject experience a sensation of darkness at home? (yes/no)
19. Are there obstacles that the subject must avoid in the corridor, living room or entryway? (yes/no)
20. Are there steps in the subject's house? (yes/no)
21. Does the subject have to use steps? (yes/no)
22. Does the subject walk along steep slopes near to his/her home in his/her daily life? (yes/no)

Appendix 3 Frailty Assessment[24),25)]

Survey the following items and enter them on the case report form.

Item	Details
Weight loss	If the subject answers "yes" to the question "Have you (unintentionally) lost 2 to 3 kg or more in the past 6 months?"
Exhaustion	If the subject answers "yes" to the question "In the last 2 weeks, have you felt tired for no reason?"
Activity level	If the subject answers "I do not do exercise" to both of the following questions: Approximately how many days per week do you engage in low levels of physical exercise (including farm work)? Approximately how many days per week do you engage in moderate levels of physical exercise or sports (including farm work)?
Grip strength	(Measured in the dominant hand) < 26 kg for men or < 18 kg for women
Comfortable walking speed	(Measure the time taken to walk a measurement section with a length of 5 m, with a lead-in section of 1 m before and after the measured section.) If the speed is < 1 m/s.

Appendix 4 One-leg Standing Test with Eyes Open[26)]

Conduct a test according to the following procedure, and enter the results of the test on the case report form.

1. Preparation

Stopwatch

2. Method
   I. The subject is to take the test in bare feet.
   II. The subject places both hands on his/her hips, and stands on one leg at a time, trying each leg to check which one is easiest to stand on.
   III. When the subject has chosen a leg to stand on, he/she puts his/her hands on his/her hips, and upon being told to "raise one leg," assumes a one-legged stance.

3. Records
   I. Measure the duration of the time for which the subject maintains the one-legged stance. End the test if the subject continues to maintain the one-legged stance for 120 seconds.
   II. Record times in seconds, rounding down fractions of a second.
   III. Conduct the test twice and record the better score out of the two tests. (If the first result is 120 seconds, do not conduct the test a second time.)

4. Precautions about conducting the test.
   I. Conduct the test on a non-slip floor.
   II. Do not place objects near the subject undergoing the test. Avoid locations with stairs or slopes.
   III. Before the test, inform the subject undergoing the test of the following.
      A) The task in this test is to stand on one leg for as long as possible.
      B) The stance for standing on one leg is to keep the knee of the supporting leg straight, and raise the other leg up so that it does not touch the supporting leg.
      C) The conditions for ending the test are:
         i. If the leg being lifted up touches the ground or the supporting leg
         ii. If the position of the supporting leg shifts
         iii. If the subject takes one or both hands off his/her hips.
      D) Since saying "start" is enough to make some people lose their balance, it is

better to start by saying “raise one leg” and measure the time starting from when the subject stands on one leg.

E) The person doing the measurement will be ready to support the subject undergoing the test immediately if he/she loses his/her balance.

F) The conditions for ending the tests will be strictly adhered to. It is advisable to allow the subject undertaking the test to practice first.