Study Protocol

허혈성 뇌졸중 환자에서 **Cytochrome P450 2C19** 유전자형에 따른 **Clopidogrel** 의 주요 혈관질환 발생 예방 효과에 대한 다기관, 전향적 관찰 연구

A multicenter Prospective observationaL study to evAluate the effecT of clopidogrel on the prEvention of major vascuLar events according to the gEnotype of cytochrome P450 2C19 in ischemic stroke paTients (PLATELET study)

Sponsor:	Department of Neurology, Gangnam Severance Hospital Professor Lee Kyung-Yeol
Study protocol number:	PLATELET-001
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Research phase:	Investigator-initiated prospective study

[Study Protocol Version History]

No	Version No. (Date)	Amendments
1	Ver.1.0 (30JUL2019)	Not Applicable

2	Ver.1.1 (08OCT2019)	・ Changing phrasing around study monitoring ・ Changing phrasing of the human consent process ・ Changing unnatural expressions ・ Deleting items related to study institutions and the principal investigator ・ Deleting Attachment 1 (Testing Organization and Principal Investigator) and Attachment 4 (Principal Investigator Signature Page)
3	Ver.1.2 (18OCT2021)	・ Changing the clinical trial period

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[Summary of the Study Protocol]

Study Title	허혈성 뇌졸중 환자에서 **Cytochrome P450 2C19** 유전자형에 따른 **Clopidogrel** 의 주요 혈관질환 발생 예방 효과에 대한 다기관, 전향적 관찰 연구 A multicenter Prospective observationaL study to evAluate the effecT of clopidogrel on the prEvention of major vascuLar events according to the gEnotype of cytochrome P450 2C19 in ischemic stroke paTients (PLATELET study)
Study phase	Prospective observational study
Target condition	Ischemic stroke
Study protocol number	PLATELET-001
Objectives	This study aims to test the hypothesis that poor metabolizers and intermediate metabolizers of cytochrome P450 2C19 genotypes will have a higher risk of composite cardiovascular events, including recurrent stroke, than extensive metabolizers, among patients with acute ischemic stroke receiving clopidogrel.
Sponsor / study coordinator	Professor Lee Kyung-yeol, Department of Neurology, Gangnam Severance Hospital
Funding organization	Samjin Pharmaceutical
Testing organization	Synex
Number of subjects	A total of 2,927 patients with ischemic stroke who received clopidogrel within 72 hours after the onset of symptoms will be enrolled in the study to ensure statistical significance. Each organization will be initially allocated 30 spots, followed by competitive enrollment.
Rationale for the calculation of the number of subjects	This study will enroll patients with ischemic stroke who have received clopidogrel within 72 hours after the onset of symptoms, with a total enrollment of 2,927 patients. In the CAPRIE study, the incidence of cardiovascular events (composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death) in the clopidogrel group was 5.32% per year. A meta-analysis comparing the risk of composite cardiovascular events according to cytochrome P450 2C19 genotype distribution with clopidogrel treatment in patients with acute cerebral infarction and TIA found that the risk of composite cardiovascular events in poor and intermediate metabolizers was approximately 1.51 times higher than in extensive metabolizers. Considering existing national reports on Cytochrome P450 2C19 genotype distribution, poor metabolizers and intermediate metabolizers are estimated to account for 60% of all subjects, with the remaining 40% being extensive metabolizers. Based on these previous findings, the 6-month incidence of composite cardiovascular events, the primary objective of this study, was set at 3% for extensive metabolizers and 4.5% for low and intermediate metabolizers. The number of subjects required to test the hypothesis that event-free survival at 6-month follow-up is equal in the two groups according to the study protocol with a two-sided long-rank test, alpha = 0.05, 1-beta (power) = 0.8 is 2,634 in total, with 1,053 extensive metabolizers and 1,581 poor and intermediate metabolizers. Based on a 10% drop-out rate, a total of 2,927 subjects are needed to complete the study.

Period	From the start date through December 31, 2023
Design	Prospective, multicenter, observational study
Methods	This is a multicenter, observational study to determine whether there are differences in composite cardiovascular events, i.e., recurrent stroke (ischemic and hemorrhagic), myocardial infarction, and cardiovascular death, in patients with ischemic stroke who are poor or intermediate metabolizers compared to extensive metabolizers based on the cytochrome P450 2C19 genotype. Patients with acute ischemic stroke who have received 75 mg to 300 mg (for loading dose) of clopidogrel within 72 hours after the onset of the event, who have undergone cytochrome P450 2C19 genotyping prior to study enrollment, and who meet the inclusion and exclusion criteria, will be enrolled in this study after the investigator fully explains the study protocol to the patient and their legal guardians and obtains written informed consent. In this study, the time of stroke onset is based on the time of first neurologic abnormality due to stroke, but if the patient wakes up and notices symptoms or the exact time of stroke onset is difficult to determine, it is defined as the last normal time. Since this is an observational study and not a randomized study, there are no restrictions on the method of administration for clopidogrel. However, concomitant use of aspirin and antiplatelet agents other than clopidogrel is restricted, and the administration of clopidogrel will be maintained until the end of the study. Based on the results of the cytochrome P450 2C19 genotyping, the subjects will be divided into two groups, poor or intermediate metabolizers and extensive metabolizers, and analyzed for differences in composite cardiovascular events, i.e., recurrent stroke (ischemic and hemorrhagic), myocardial infarction, and cardiovascular death, in patients with ischemic stroke. The subjects will be asked to visit the hospital at 1, 3, and 6 months after the initiation of clopidogrel administration and will be investigated for the occurrence of any adverse events and adverse drug reactions corresponding to the endpoints at these visits.
Test drug	Clopidogrel 75 mg
Inclusion and exclusion criteria	**<u>Inclusion criteria</u>** 1) Patients with a confirmed ischemic stroke via brain CT or MRI 2) Patients who received clopidogrel within 72 hours after the onset of ischemic stroke* 3) Adults aged 19 or older 4) Patients who agree to participate in this study within 7 days of the onset of ischemic stroke* 5) Patients who have undergone cytochrome P450 2C19 genotyping * In this study, the time of stroke onset is based on the time of first neurologic abnormality due to stroke, but if the patient wakes up and notices symptoms or the exact time of stroke onset is difficult to determine, it is defined as the last normal time. **<u>Exclusion criteria</u>** 1) Patients taking oral anticoagulants at screening or scheduled to start taking them within 6 months 2) Patients who need to use antiplatelets other than aspirin and clopidogrel 3) Patients with a history of taking clopidogrel 1 week prior to the onset of ischemic stroke

	4) Patients scheduled for coronary angioplasty and stenting, CABG, carotid endarterectomy, or cerebral artery stenting within 6 months 5) Patients with severe comorbidities or a diagnosis of untreated malignancy who have a life expectancy of less than 2 years 6) Patients who have participated in another drug clinical trial within the past 30 days 7) Patients with TOAST classification findings of high-risk factors for cardiogenic embolism 8) Any other patients who, in the judgment of the investigator, are expected to have difficulty participating and continuing in this study
Clinical endpoints	• **Primary endpoints** The primary endpoint of this study is the incidence of composite cardiovascular events. To test the study hypothesis, it is intended to determine whether there is a difference in the incidence of composite cardiovascular events between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype. A composite cardiovascular event is defined as any of the following three events: 1. Recurrent stroke A stroke is defined as a focal neurologic abnormality caused by a blood vessel in the brain that has lasted for more than 24 hours, or a finding of stroke consistent with symptoms on a brain imaging test performed after the onset of symptoms, even if the abnormality has not lasted for more than 24 hours. Stroke is ischemic or hemorrhagic based on the findings of brain imaging tests. Meanwhile, stroke for which brain imaging tests have not been performed or the results are unclear is defined as other undefined strokes. 2. Onset of myocardial infarction It is a typical elevation or gradual decrease in the myocardial marker troponin or a rapid elevation or decrease in CK-MB, accompanied by one of the following: 1) Symptoms of myocardial ischemia 2) Development of pathologic Q waves on the electrocardiogram 3) Elevation or depression of the ST segment or new left bundle branch block (LBBB) indicative of ischemia on the ECG 4) Additional loss of viable myocardium or new onset of regional myocardial wall motion disturbance 5) Identification of an intracoronary thrombus on coronary angiography 3. Cardiovascular death Fatal stroke, fatal myocardial infarction, and sudden death not clearly identified as nonvascular • **Secondary endpoints** At follow-up, it is intended to determine if there is a difference in the following endpoints between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype.

	1. Ischemic stroke 2. Transient cerebral ischemia (TIA) with no ischemic lesion identified on diffusion-weighted imaging (DWI) of the brain 3. Revascularization (cerebral, coronary, aortic, and peripheral arteries) 4. Myocardial infarction (if the criteria for the primary endpoint above are met) 5. Worsening of early neurologic symptoms (NIHSS total score increased by 2 or more points within 7 days after the onset of symptoms) 6. Percentage of mRS 0-2 at 3 months from the onset of symptoms • **Tertiary endpoints** 1. Major bleeding (fatal bleeding, symptomatic cerebral hemorrhage, ocular hemorrhage, incapacitating bleeding, transfusion of more than 2 packs of whole blood or red blood cells, or bleeding requiring hospitalization) 2. All-cause mortality
Data analysis and statistical analysis methods	**General principles** This is an observational study in which data from all patients who have given consent to participate will be used for analysis. As it is an observational study, there is no separation of the intention to treat and per protocol groups, and data from all patients who meet the inclusion and exclusion criteria and agree to participate in the study will be used. The analysis set is defined as all subjects who have received clopidogrel within 72 hours after the onset of ischemic stroke and who have given consent to participate in the study. Continuous data is represented by mean and standard deviation, while categorical data is represented by frequency and percentage. To compare groups, Student's t-test, paired t-test, and analysis of variance are used for continuous data, and Chi square test and Fisher's exact test are used for categorical data. When data distribution assumptions of parametric tests are not met, an appropriate nonparametric test method is used. **Analysis for primary endpoints** A log-rank test is used to determine if there is a difference in the incidence of composite cardiovascular events between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype. The analysis set is all patients who meet the inclusion and exclusion criteria and consent to participate in the study, with a significance level of 5% using a two-tailed test. **Analysis for secondary and tertiary endpoints** As with the analysis for the primary endpoint, a log-rank test is used to determine if there is a difference in the incidence of events for the secondary and tertiary endpoints between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype. The analysis set is all patients who meet the inclusion and exclusion criteria and consent to participate in the study, with a significance level of 5% using a two-tailed test.

[Schedule]

Period	Screening visit	Follow-up visit (or phone call)		
Visit	**Screening Visit[2]**	**Visit 1**	**Visit 2**	**Visit 3 (EOS)[18]**
Week (±Visit Window)	**Day 1**	**4 Weeks (±14d)**	**12 Weeks (±28d)**	**24 Weeks (±28d)**
Informed consent[1]	O			
Baseline information[3]	O			
Vital signs (blood pressure, pulse)[4]	O	O	O	O
Smoking history and status[5]	O	O	O	O
Medical history[6]	O			
Stroke information	O			
Inclusion and exclusion criteria	O			
TOAST classification	O			
Laboratory test[7,10]	O			
CYP2C19 genotyping[10]	O			
Brain image[8]	O			
Heart tests[9,10]	O			
NIHSS[11]	O			
mRS	O[12]	O	O	O
Determining study continuation and dropout		O	O	O
Antiplatelet medication history[13]		O	O	O
Thrombolysis[14]	O			
Checking for prior/concomitant medications[15]	O[15]	O	O	O
Hospitalization history[16]	O			
Checking for the endpoints		O	O	O
Checking for adverse events[17]		O	O	O

1. A written consent shall be obtained from the subject prior to conducting any procedure.
2. The subjects are enrolled based on the data collected during the screening visit to determine if they meet the final inclusion and exclusion criteria.
3. At the screening visit, their date of birth, gender, height, weight, and body mass index (BMI)* are collected.
4. Vital signs are collected at each visit for blood pressure and pulse.
5. At the screening visit, their smoking history is taken, and at subsequent follow-up visits (Visits 1-3), their smoking status is monitored.
6. At the screening visit, their history of the following conditions are checked:
   - hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary artery disease (myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery), transient ischemic attack (TIA), cerebral infarction, cerebral hemorrhage, unclassified stroke (cerebral infarction or cerebral hemorrhage), and cancer.
7. The laboratory test collects the following items:

Hematology	White blood cell count, Neutrophil count, Lymphocyte count, hemoglobin, hematocrit, platelet count, red blood cell distribution width, mean platelet volume
Serum biochemistry	Glucose (initial, fasting), BUN, Creatinine, eGFR (MDRD)*, AST, ALT, HbA1c, Total cholesterol, HDL-cholesterol, LDL cholesterol, Triglyceride
Immunoassay	CRP or hs-CRP
Coagulation test	aPTT, INR, D-dimer, Platelet drug response assay (VerifyNow PRU test)

8. Whether a brain image (MRI, MRA, CT, CTA, DSA) has been performed and the results are checked. The results of brain image tests performed after the onset of ischemic stroke but before Visit 1 are used.

9. Heart tests include an electrocardiogram, echocardiogram (TEE/TTE), and Holter test.
10. The results of laboratory tests, CYP2C19 genotyping, and electrocardiograms are collected after the onset of stroke.
11. The NIHSS is collected daily during the hospital stay until discharge if discharged on or before post-admission day 7.
12. At the screening visit, two mRS are collected: the mRS before the onset of stroke (baseline mRS) and the mRS at discharge. If the time of discharge is after Visit 1, it is not necessary to collect the mRS at discharge.
13. At the screening visit, the prior use of antiplatelets is checked, and the doses of clopidogrel and aspirin are checked at subsequent follow-up visits.
14. At the screening visit, prior thrombolysis is checked.
    - Intravenous (IV) thrombolysis: Whether intravenous tissue plasminogen activator (t-PA) therapy has been performed
    - Intra-arterial (IA) thrombectomy: Whether mechanical thrombectomy has been performed
15. Prior medications are only checked at the screening visit, and the criteria for collecting prior and concomitant medications are as follows:
    - Prior medications: Antiplatelet medications, oral anticoagulants, antihypertensives, oral diabetes medications, insulin, and statins taken within 1 week prior to the onset of stroke
    - Concomitant medications : Antiplatelet medications, antihypertensives, oral diabetes medications, insulin, and statins taken after the onset of stroke
16. As for hospitalization history, the admission date, discharge date, and discharge type are checked.
17. This study will only collect serious adverse events.
18. In the event of an early termination, the reason shall be verified, followed by the same procedure as Visit 3 (end -of-study, EOS).

* Body mass index and eGFR values are calculated automatically by the electronic data capture (EDC) system using the equation.

[Abbreviations and terminology definitions]

ADP	Adenosin Di-Phosphate
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK-MB	Creatine kinase-MB fraction
CRF/eCRF	Case Report Form/Electronic Case Report Form
CRP	C-reactive protein
CT	Computerized Tomography
CTA	Computerized Tomographic Angiography
CYP2C19	Cytochrome P450 2C19
DSA	Digital Subtraction Angiography
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
HbA1c	Hemoglobin A1c
IA	Intra-Arterial
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LBBB	Left Bundle Branch Block
LDL	Low Density Lipoprotein
MDRD	Modification of Diet in Renal Disease
mg	Milligram
mg/dL	Milligrams/deciliter
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale

PRU	Platelet Reactivity Unit
QD	Quaque Die(Every day)
SAE	Serious Adverse Event
SGOT (AST)	Serum Glutamate-Oxaloacetate-Transaminase (Aspartate Aminotransferase)
SGPT (ALT)	Serum Glutamate-Pyruvate-Transaminase (Alanine Aminotransferase)
SOP	Standard Operating Procedure
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TOAST classification	Trial of ORG 10172 in Acute Stroke Treatment classification
t-PA	Tissue Plasminogen Activator
TTE	Transthoracic Echocardiography
WBC	White Blood Cell/Count

1. Study Title and Phase

1.1. Study Title

허혈성 뇌졸중 환자에서 Cytochrome P450 2C19 유전자형에 따른 Clopidogrel 의 주요 혈관질환 발생 예방 효과에 대한 다기관, 전향적 관찰 연구

A multicenter Prospective observationaL study to evAluate the effecT of clopidogrel on the prEvention of major vascuLar events according to the gEnotype of cytochrome P450 2C19 in ischemic stroke paTients; PLATELET study

1.2. Study phase

Prospective observational study

2. Name and title of the study coordinator

Study coordinator: Professor Lee Kyung-Yeol, Department of Neurology, Gangnam Severance Hospital

3. Name and address of the sponsor

Sponsor	Professor Lee Kyung-Yeol, Department of Neurology, Gangnam Severance Hospital
Address	211, Eonju-ro, Gangnam-gu, Seoul, Korea

4. Name and address of the funding organization

Funding organization	Samjin Pharmaceutical
Address	121, Wausan-ro, Mapo-gu, Seoul, Korea

5. Name and address of the testing organization

Testing organization	Synex
Address	10F, Asea Tower, 430, Nonhyeon-ro, Gangnam-gu, Seoul, Republic of Korea

6. Introduction

6.1. Background and rationale of the study

Clopidogrel, an antiplatelet used for secondary prevention in patients with ischemic stroke and coronary artery disease, has been shown to have a superior antithrombotic effect compared to aspirin and is therefore administered to many patients with stroke and coronary artery disease. Clopidogrel exerts its antithrombotic effects as the active metabolite, which is metabolized in the liver, inhibits P2Y12, an ADP receptor on platelets, thereby interfering with platelet aggregation. As for resistance to clopidogrel with these pharmacokinetics, it has been suggested that drugs with the same metabolic pathway as clopidogrel may cause inhibitory interactions when concomitantly administered.[1-3] Leading studies such as the New England Journal of Medicine and the Lancet have reported that the genotype of cytochrome P450 2C19, which is involved in the hepatic metabolism of clopidogrel, is associated with differential response to the drug and recurrence of cardiovascular events.[4-7] Although there is some variation in the literature, the risk of recurrent ischemic stroke has been reported to be as much as four times greater for poor or intermediate metabolizers compared to extensive metabolizers based on the cytochrome P450 2C19 genotype.[8,9] Cytochrome P450 2C19 genotypes also vary by race, with Asians being more likely to be low or intermediate metabolizers.[10,11]
Previous studies of clopidogrel resistance based on the cytochrome P450 2C19 genotype have been conducted primarily in patients with coronary artery disease, with no data on stroke patients. Therefore, there are few studies on whether resistance to clopidogrel based on the cytochrome P450 2C19 genotype in stroke patients is associated with the development of composite cardiovascular events, including recurrent stroke. The hypothesis of the study was "Among patients with acute ischemic stroke, poor or intermediate drug metabolizers will at higher risk of composite cardiovascular events, including recurrent stroke, compared to extensive metabolizers based on the cytochrome P450 2C19 genotype."

7. Objectives

This study aims to test the hypothesis that among patients with acute ischemic stroke receiving clopidogrel, poor and intermediate metabolizers will be at higher risk of composite cardiovascular events, including recurrent stroke, compared to extensive metabolizers based on the cytochrome P450 2C19 genotype.

8. Inclusion and exclusion criteria, target number of subjects, and rationale

8.1. Inclusion criteria

1) Patients with a confirmed ischemic stroke via brain CT or MRI
2) Patients who received clopidogrel within 72 hours after the onset of ischemic stroke*
3) Adults aged 19 or older
4) Patients who agree to participate in this study within 7 days of the onset of ischemic stroke*
5) Patients who have undergone cytochrome P450 2C19 genotyping

* In this study, the time of onset is based on the time of first neurologic abnormality due to stroke, but if the patient wakes up and notices symptoms or the exact time of onset is difficult to determine, it is defined as the last normal time.

8.2. Exclusion criteria

1) Patients taking oral anticoagulants at screening or scheduled to start taking them within 6 months
2) Patients who need to use antiplatelets other than aspirin and clopidogrel
3) Patients with a history of taking clopidogrel within 1 week prior to the onset of ischemic stroke
4) Patients scheduled for coronary angioplasty and stenting, CABG, carotid endarterectomy, or

cerebral artery stenting within 6 months

5) Patients with severe comorbidities or a diagnosis of untreated malignancy who have a life expectancy of less than 2 years
6) Patients who have participated in another drug clinical trial within the past 30 days
7) Patients with TOAST classification findings of high-risk factors for cardiogenic embolism
8) Any other patients who, in the judgment of the investigator, are expected to have difficulty participating and continuing in this study

* In the TOAST classification, the high-risk factors for cardiogenic embolism are as follows:
- Mechanical prosthetic valve
- Mitral stenosis with atrial fibrillation
- Atrial fibrillation (excluding lone atrial fibrillation)
- Left atrial/atrial appendage thrombus
- Sick sinus syndrome
- Recent myocardial infarction (<4 weeks)
- Left ventricular thrombus
- Dilated cardiomyopathy
- Akinetic left ventricular segment
- Atrial myxoma
- Infective endocarditis

8.3. Target number of subjects and rationale

The study will enroll patients with ischemic stroke within 72 hours after the onset of symptoms, with a total enrollment of 2,927 patients. In the CAPRIE study, the incidence of cardiovascular events (composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death) in the clopidogrel group was 5.32% per year.[12] In a meta-analysis comparing the risk according to cytochrome P450 2C19 genotype distribution on clopidogrel treatment in patients with acute cerebral infarction and TIA, the risk of composite cardiovascular events is approximately 1.51 times for poor and intermediate metabolizers compared to extensive metabolizers.[8] Considering existing national reports on Cytochrome P450 2C19 genotype distribution, poor metabolizers and intermediate metabolizers are estimated to account for 60% of all subjects, with the remaining 40% being extensive metabolizers.[13] Based on these previous findings, the 6-month incidence of composite cardiovascular events, the primary objective of this study, was set at 3% for extensive metabolizers and 4.5% for low and intermediate metabolizers. The number of subjects required to test the hypothesis that event-free survival at 6-month follow-up is equal in the two groups according to the study protocol with a two-sided long-rank test, alpha = 0.05, 1-beta (power) = 0.80 is 2,634 in total, with 1,053 extensive metabolizers and 1,581 poor and intermediate metabolizers. Based on a 10% drop-out rate, a total of 2,927 subjects are needed to complete the study.

9. Test drug

9.1. Clopidogrel

1) Generic name of the primary ingredient: Clopidogrel
2) Primary ingredient and quantity of the active pharmaceutical ingredient (API): Clopidogrel hydrogen sulfate 97.875 mg
3) Usage: 75 mg once daily (QD), with or without food
4) Storage: Airtight container, room temperature (1-30℃)
5) Adverse events and precautions: The most common adverse events are upper respiratory tract infection, chest pain, headache, influenza-like symptoms, aches, joint pain, dizziness, back pain, abdominal pain, purpura, and indigestion. Overall tolerability was similar to aspirin, regardless of age, gender, or race. The frequency of patients discontinuing medication due to adverse events was roughly the same as aspirin (13%). A potential risk is increased bleeding time. Caution must be exercised when administering to patients with gastrointestinal bleeding, patients with bleeding-prone lesions (such as ulcers) or increased risk of bleeding, patients with severe hepatic disease with hemorrhagic predisposition, and patients with renal insufficiency. Rare cases of thrombotic thrombocytopenic purpura and neutropenia have been reported. It shall not be administered to

patients who are hypersensitive to this drug or any of its components, or who have pathologic bleeding such as peptic ulcer disease or intracranial hemorrhage at the time of administration, patients with severe hepatic impairment, nursing mothers, and patients with congenital galactose intolerance, lactase deficiency, or glucose-galactose malabsorption (lactose-containing formulations only).

10. Methods

10.1. Period

From the start date through December 31, 2023

10.2. Methods

This is a multicenter, observational study to determine the difference in composite cardiovascular events, recurrent stroke (ischemic and hemorrhagic), myocardial infarction, and cardiovascular death in patients with ischemic stroke between poor or intermediate metabolizers and extensive metabolizers based on the cytochrome P450 2C19 genotype.

Patients with acute ischemic stroke who have received 75 mg to 300 mg (for loading dose) of clopidogrel within 72 hours after the onset of the event, who have undergone cytochrome P450 2C19 genotyping prior to study enrollment, and who meet the inclusion and exclusion criteria, will be enrolled in this study after fully explaining the study protocol and obtaining written informed consent from the patient and their legal guardians. In this study, the time of stroke onset is based on the time of first neurologic abnormality due to stroke, but if the patient wakes up and notices symptoms or the exact time of stroke onset is difficult to determine, it is defined as the last normal time.

Based on the results of the cytochrome P450 2C19 genotyping, the subjects will be divided into two groups, poor or intermediate metabolizers and extensive metabolizers, and analyzed for differences in composite cardiovascular events, i.e., recurrent stroke (ischemic and hemorrhagic), myocardial infarction, and cardiovascular death, in patients with ischemic stroke.

The subjects will be asked to visit the hospital at 1, 3, and 6 months after the initiation of clopidogrel administration and will be investigated for the occurrence of any adverse events and adverse drug reactions corresponding to the endpoints at these visits.

10.3. Concomitant medication administration criteria and prohibited concomitant medications

Due to the nature of the conditions of the subjects in this study, they may have chronic diseases such as hypertension, hyperlipidemia, and diabetes and their complications requiring treatment. Therefore, it is not possible to have a patient discontinue relevant treatment for the purpose of enrolling them in a clinical study. Since this is an observational study and not a randomized study, there are no restrictions on the concomitant medications.

However, the following two types of medications shall not be administered during this observational study.

- Antiplatelets other than aspirin and clopidogrel
- Oral anticoagulants

10.4. Rescue medications and additional treatments

This is an observational study involving no rescue medication. No additional medications are provided as part of this study.

10.5. Medication adherence

At each visit, the antiplatelet prescription shall be checked.

11. Discontinuation and dropout criteria

11.1. Temporary discontinuation of the test drug administration

The test drug administration may be temporarily stopped without the subject dropping out of the study under the following circumstances:

1) Discontinuing to perform surgery and diagnostic testing planned before participation in the study
2) Occurrence of an adverse event requiring temporary discontinuation of the test drug administration, as determined by the investigator
3) Surgery or procedure during participation in the study requiring temporary discontinuation of the test drug administration, as determined by the investigator

In the event of temporary discontinuation, the investigator shall make the final judgment as to the feasibility and timing of resuming clopidogrel administration. If discontinuation is due to an adverse event, permanent discontinuation of the test drug and withdrawal of the subject from the study shall be considered with persistent symptoms that do not improve.

11.2. Discontinuation and dropout criteria

The investigator shall encourage the subjects to comply with the test drug and adhere to the protocol-related procedures. The subjects also have the right to withdraw from the study at any time for any reason.

The study may be discontinued for the subjects in the following circumstances:

- Withdrawal of consent from subjects
- Investigator judgment
    - Violation of inclusion or exclusion criteria
    - Serious adverse events
    - Worsening of underlying medical condition
    - Subject's refusal of treatment
    - Other reasons for discontinuation in the judgment of the investigator

Non-adherence to clopidogrel, concomitant medications, or missed visits do not constitute reasons for dropping out of the study and will be judged by the investigator on a case-by-case basis.

If an event that meets the primary endpoint occurs during the course of the study, participation in the study will be considered complete, followed by procedures equivalent to the EOS visit.

If new clinical guidelines for the administration of clopidogrel based on the drug metabolizing enzyme genotype in patients with stroke are published during this study, they shall be followed for the safety of the subjects, and, in some cases, the study may be terminated early.

The EOS procedures shall be followed for all subjects, including those who drop out early.

12. Observation items and visit procedures

12.1. Observation items

12.1.1. Written consent and confirmation of inclusion and exclusion criteria

After reviewing the inclusion and exclusion criteria, the subjects who meet the criteria will be given a detailed explanation of the purpose and content of the study by the principal investigator, and the written consent will be dated and signed by the subjects or their legal guardians. After obtaining written consent, each subject is assigned a subject identification number.

Subject identification numbers are assigned in the order of obtaining written consent. The first two digits of the subject identification number "□□R - □□□□" represent the institutional number, "R" represents registration, and the last four digits represent the order in which written informed consent is obtained. For example, 01R-0002 refers to a subject who has given written consent for the second time to an institution with institution number 01.

12.1.2. Basic information

At the screening visit, the following items will be examined:

- Written consent status
- Written consent date
- Subject identification number
- Demographic information: Date of birth, gender, height, weight, body mass index*

*BMI (kg/m^2) is automatically calculated using the equation below.

$BMI = W / H^2$ (kg/m^2)
W: Weight (kg)
H: Height (m)

12.1.3. Smoking history and status

At the screening visit, the smoking history is obtained, and at subsequent follow-up visits (Visits 1-3), their smoking status is monitored.

- Smoking history (screening): smoking amount per day (packs) and duration of smoking (year)
- Smoking status (Visits 1-3)

12.1.4. Medical history

At the screening visit, their history of the following conditions are checked:

- The definitions of hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary artery disease (myocardial infarction, unstable angina, PCI, and CABG surgery), TIA, cerebral infarction, cerebral hemorrhage, unclassified stroke (cerebral infarction or cerebral hemorrhage), and cancer are provided in Attachment 1.

12.1.5. Stroke information

At the screening visit, information on ischemic strokes that have occurred within 7 days is collected.

- Date of stroke onset (last normal time)
- Date of visit
- Date of first administration of clopidogrel after the onset of stroke

12.1.6. Cytochrome P450 2C19 genotyping

As this is an observational study conducted in a real-world clinical setting, the results of tests deemed necessary by the principal investigator to be relevant to the diagnosis and treatment of the target condition will be collected.

- Genotyping status
- CYP2C19 Allele Type

Cytochrome P450 2C19 genotyping typically looks at the *1, *2, and *3 alleles, with those with *1/*1 defined as extensive metabolizers, those with only one *2 or *3 defined as intermediate metabolizers (*1/*2, *1/*3), and those with two *2 or *3 defined as poor metabolizers (*2/*2, *2/*3, *3/*3). If some institutions test for the *17 allele, *1/*17 and *17/*17 are included as extensive metabolizers and *2/*17 and *3/*17 as intermediate metabolizers.

Metabolizer classification	**CYP2C19 Allele Type**
Extensive metabolizers	*1/*1, *1/*17, *17/*17
Intermediate metabolizers	*1/*2, *1/*3, *2/*17, *3/*17
Poor metabolizers	*2/*2, *2/*3, *3/*3

12.1.7. Vital signs and laboratory tests

- Vital signs: Pulse and blood pressure
- Laboratory tests: The results of the following tests will be collected only if they have been performed in actual practice, with no additional tests performed for the purpose of this study.

Hematology	White blood cell count, Neutrophil count, Lymphocyte count, hemoglobin, hematocrit, platelet count, red blood cell distribution width, mean platelet volume
Serum biochemistry	Glucose(initial, fasting), BUN, Creatinine, eGFR(MDRD)*, AST, ALT, HbA1c, Total cholesterol, HDL-cholesterol, LDL cholesterol, Triglyceride
Immunoassay	CRP or hs-CRP
Coagulation test	aPTT, INR, D-dimer, Platelet drug response assay (VerifyNow PRU test)

* The eGFR value is automatically calculated for EDC using the MDRD equation below.

$$eGFR\ (mL/min/1.73\ m^2) = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203}\ (\times 0.742, \text{for women})$$

12.1.8. Prior and concomitant medications

Prior medications are only checked at the screening visit, and the criteria for collecting prior and concomitant medications are as follows:

1) Prior medications: Administered within 1 week before the onset of stroke

- Antiplatelets: Aspirin, clopidogrel, cilostazol, triflusal, ticlopidine, dipyridamole, ticagrelor, prasugrel
- Oral anticoagulants
- Antihypertensives: Salcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, diuretics, alpha blocker
- Oral diabetes medications
- Insulin

- Statins: Product name, dose (daily dose)

2) Concomitant medications: Administered after the onset of stroke

- Antiplatelets: Cilostazol, triflusal, ticlopidine, dipyridamole, ticagrelor, prasugrel
- Antihypertensives: Calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, diuretics, alpha blocker
- Oral diabetes medications
- Insulin
- Statins: Product name, dose (daily dose)

12.1.9. Antiplatelet medication history

At the follow-up visits, the doses of clopidogrel and aspirin are checked.

- Antiplatelet type: Aspirin and clopidogrel
- Dose: Total daily dose and prescription days

12.1.10. Thrombolysis

At the screening visit, whether thrombolysis has been performed is checked.

- IV thrombolysis: Whether intravenous tissue plasminogen activator (t-PA) therapy has been performed
- Intra-arterial (IA) thrombectomy: Whether mechanical thrombectomy has been performed

12.1.11. Hospitalization history

- Admission date
- Discharge date
- Discharge type: Transferred to another department, discharged to home, transferred to another hospital, deceased

12.1.12. Brain image

Whether a brain image (MRI, MRA, CT, CTA, DSA) has been performed and the results are checked. In addition, any stenosis or occlusion of 50% or greater in the relevant cerebral artery associated with the infarct site is identified on angiography. The results of brain image tests performed after the onset of ischemic stroke but before Visit 1 are used.

12.1.13. Heart tests:

Whether heart tests have been performed is checked.

- Electrocardiogram, echocardiogram (TEE/TTE), Holter test

12.1.14. TOAST classification

The subjects are assessed based on the TOAST classification.

- Large artery atherosclerosis
- Cardioembolism
- Lacunar infarction
- Stroke of other determined
- Stroke of undetermined (two or more cause, negative evaluation, incomplete evaluation)

12.1.15. Inclusion and exclusion criteria

The final assessment of eligibility for the study will be made by evaluating whether subjects who meet the inclusion and exclusion criteria in Sections 8.1 and 8.2 have been selected based on their consent status as well as baseline information, stroke information, medical history, prior and concomitant medications, antiplatelet medication history, genotyping, TOAST classification, laboratory tests, and brain images.

12.1.16. National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) is a scale used to measure the severity of neurological deficit symptoms. It is a 15-item scale for 11 factors, with a score of 0 being normal and the highest score being 42. Depending on the symptoms, a higher score indicates a more severe disability. The scale is attached in Attachment 1.

12.1.17. Modified Rankin Scale

The Modified Rankin Scale (mRS) is a scale used to measure a patient's overall level of disability after the onset of stroke. Symptoms are scored on a scale from 0 to 6, with 0 indicating no impairment at all and a higher score indicating more severe impairment. The scale is attached in Attachment 2.

12.2. Visit procedures

12.2.1. Screening visit (Day 1)

The following procedures and assessments are performed during the screening visit:

1) Obtaining written consent
2) Assigning subject identification number
3) Basic information survey: Date of birth, gender, height, weight, BMI
4) Smoking history
5) Vital signs: Blood pressure and pulse
6) Medical history
7) Stroke information
8) Prior and concomitant medications
9) Brain image
10) Laboratory tests
11) CYP2C19 genotyping
12) Heart test status
13) TOAST classification
14) NIHSS test (for 7 post-admission days or daily until discharge if discharged within 7 days)
15) mRS test: mRS before the onset of stroke (baseline mRS) and mRS at discharge (transfer) (if discharged after Visit 1, it is not necessary to collect mRS at discharge).
16) Thrombolysis status
17) Evaluation of inclusion and exclusion criteria

12.2.2. Follow-up visits (Visits 1 to 3)

The following procedures and assessments are performed at follow-up visits at week 4 (Visit 1), week 12 (Visit 2), and week 36 (Visit 3). Visit 3 is the EOS visit, where all subjects, including dropouts, undergo the procedures of the EOS procedures.

1) Vital signs: Blood pressure and pulse
2) Checking smoking history
3) Checking for the endpoints

4) Checking prior and concomitant medications
5) Checking for adverse events
6) mRS test
7) Checking antiplatelet medication history

If subjects are unable to make the visit, the visit can be replaced with a follow-up phone call. Follow-up phone calls shall confirm occurrence of endpoints and check mRS.

12.2.3. Unscheduled visits

If, during the course of the study, the subjects visit the hospital outside of the planned visit, the following tests and assessments shall be performed to determine the condition of the subjects. All data related to adverse events shall be documented in the supporting documentation and case report. No tests or evaluations shall be performed if the subjects visit for reasons other than an adverse event.

1) Vital signs: Blood pressure and pulse
2) Checking for the endpoints
3) Checking prior and concomitant medications
4) Checking for adverse events

13. Clinical endpoints and statistical analysis methods

13.1. Clinical endpoints

13.1.1. Primary endpoints

The primary endpoint of this study is the incidence of composite cardiovascular events.

To test the study hypothesis, it is intended to determine whether there is a difference in the incidence of composite cardiovascular events between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype.

A composite cardiovascular event is defined as any of the following three events:

1. Recurrent stroke

A stroke is defined as a focal neurologic abnormality caused by a blood vessel in the brain that has lasted for more than 24 hours, or a finding of stroke consistent with symptoms on a brain imaging test performed after the onset of symptoms, even if the abnormality has not lasted for more than 24 hours. Stroke is divided into ischemic and hemorrhagic strokes based on the findings of brain imaging tests, and those for which brain imaging tests have not been performed or the results are unclear are defined as other undefined strokes.

2. Onset of myocardial infarction

It is a typical elevation or gradual decrease in the myocardial marker troponin or a rapid elevation or decrease in CK-MB, accompanied by one of the following:

1) Symptoms of myocardial ischemia
2) Development of pathologic Q waves on the electrocardiogram
3) Elevation or depression of the ST segment or new left bundle branch block (LBBB) indicative of ischemia on the ECG
4) Additional loss of viable myocardium or new onset of regional myocardial wall motion disturbance
5) Identification of an intracoronary thrombus on coronary angiography

3. Cardiovascular death

Fatal stroke, fatal myocardial infarction, and sudden death not clearly identified as nonvascular

13.1.2. Secondary endpoints

At follow-up, it is intended to determine if there is a difference in the following endpoints between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype.

1. Ischemic stroke
2. TIA with no ischemic lesion identified on diffusion-weighted imaging (DWI) of the brain
3. Revascularization (cerebral, coronary, aortic, and peripheral arteries)
4. Myocardial infarction (if the criteria for the primary endpoint above are met)
5. Worsening of early neurologic symptoms (NIHSS total score increased by 2 or more points within 7 days after the onset of symptoms)
6. Percentage of mRS 0-2 at 3 months from the onset of symptoms

13.1.3. Tertiary endpoints

1. Major bleeding
   Fatal bleeding, symptomatic cerebral hemorrhage, ocular hemorrhage, incapacitating bleeding, transfusion of more than 2 packs of whole blood or red blood cells, or bleeding requiring hospitalization

2. All-cause mortality

13.1.4. Determining the primary, secondary, and tertiary endpoints

If the primary, secondary, and tertiary endpoints occur, the investigator must send the imaging data, laboratory findings, medical records, etc. that can confirm the occurrence of the endpoints to the Steering Committee within one week of recognizing the occurrence of the endpoints, after removing the personal information (name, resident registration number, hospital registration number) of the subjects, and two or more judges must verify and recognize it.

13.2. Statistical analysis methods

13.2.1. General principles

This is an observational study in which data from all patients who have given consent to participate in the study will be used for analysis. As it is an observational study, there is no separation of the intention to treat and per protocol groups, and data from all patients who meet the inclusion and exclusion criteria and agree to participate in the study will be used. The analysis set is defined as all subjects who have received clopidogrel within 72 hours after the onset of ischemic stroke and who have given consent to participate in the study.
Continuous data is represented by mean and standard deviation, while categorical data is represented by frequency and percentage. To compare groups, Student's t-test, paired t-test, and analysis of variance are used for continuous data, and Chi square test and Fisher's exact test are used for categorical data. When data distribution assumptions of parametric tests are not met, an appropriate nonparametric test method is used.

13.2.2. Analysis for primary endpoints

A log-rank test is used to determine if there is a difference in the incidence of composite cardiovascular events between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype. The analysis set is all patients who meet the inclusion and exclusion criteria and consent to participate in the study, with a significance level of 5% using a two-tailed test.

13.2.3. Analysis for secondary and tertiary endpoints

As with the analysis for the primary endpoint, a log-rank test is used to determine if there is a difference in the incidence of events for the secondary and tertiary endpoints between patients who are poor or intermediate metabolizers and patients who are extensive metabolizers based on the cytochrome P450 2C19 genotype. The analysis set is all patients who meet the inclusion and exclusion criteria and consent to participate in the study, with a significance level of 5% using a two-tailed test.

14. Safety criteria and reporting methods, including adverse events

This is an observational study in patients taking a commercially available drug according to its labeling, and only serious adverse events will be collected and reported.

14.1. Serious adverse events

14.1.1. Definition of a serious adverse event

A serious adverse event/adverse drug reaction (AE/ADR) is an adverse event or adverse drug reaction that occurs at any dose of the test drug and meets any of the following criteria:

1) Death or life threatening events
2) Need for hospitalization or extended hospital stay
3) Permanent or significant disability and reduced functionality
4) Malformations or abnormalities in the fetus
5) In addition to cases 1) through 4), other medically significant circumstances, such as the development of substance dependence or abuse or a blood disorder

For the purposes of this study, events defined by the endpoints shall be reported as serious adverse events if they occur and meet the criteria listed above. Furthermore, if a situation occurs that is medically considered to have a significant impact on the safety and health status of the research subjects, even if it is not one of the above, the medical judgment of the investigator and relevant experts shall determine whether it is considered a serious adverse event and take appropriate measures accordingly.

Furthermore, any of the following are not considered serious adverse events:

- Voluntary and unnecessary hospitalization
- Hospitalization or extended hospital stay for technical, practical, or social reasons without an adverse event
- Hospitalization for surgery, tests, or other procedures planned before participation in the study
- Worsening of underlying medical condition

14.1.2. Reporting of serious adverse events

All serious adverse events, whether or not related to the medication being used in this study, shall be reported to the sponsor within 3 working days from the time the principal investigator becomes aware of them. Also, it shall be reported to the IRB as soon as possible according to the IRB standard operating procedure (SOP)of each institution. At the initial reporting, the principal investigator shall report as much data as can be collected, including an assessment of possible current medical conditions and serious adverse events and their causal relationship to clopidogrel.

15. Case reports

15.1. Case report guidelines and procedures

The electronic case report form (eCRF) is filled out by the principal investigator or a person authorized by the principal investigator and shall be entered as soon as possible after the visit of the subject. The research question shall be answered, with no fields left blank. Therefore, if an inspection or assessment has not been conducted or is not possible, or if the question is irrelevant (e.g., N/A), it shall be indicated according to the data input guidelines.
Furthermore, any changes or modifications to the eCRF shall be verified with the data before being modified, and the modifier, date and time of the modification, and reason for the change shall be recorded in the system. The principal investigator shall ensure that all information is consistent with the supporting documentation and shall record an explanation for any discrepancies or omissions between the supporting documentation and the eCRF.
All completed eCRFs shall be reviewed for accuracy and consistency by the principal investigator at the end of the study before final electronic signature. If necessary, a query shall be issued on the eCRF to resolve any problems with the records, and the principal investigator shall correct the data or leave a response after reviewing it.

15.2 Study monitoring

Monitoring of the study involves visits to the study center by a sponsor-appointed monitor to review the eCRFs, supporting documentation, and drug prescriptions to ensure that the protocol is being followed and that all issues are being recorded. During the visits, the monitor basically checks the subject's supporting documentation, the investigator's file, etc.
In this study, a supporting document is defined as any document that contains the evidence of the study subjects. Therefore, patient records, outcome sheets, and computerized data are acceptable as supporting documentation. The supporting documentation shall be clear and legible at any time, in accordance with ICH-GCP, and shall be the first documentation recorded at the same time as the study was conducted.
The monitor shall be provided with direct access to supporting documentation, and the investigator will cooperate with the process and location for doing so. The monitor shall review the medical records and other supporting documentation of the subject to check for consistency and/or to identify omissions against the eCRF and shall confirm any discrepancies with the investigator.

16. Storage and retrieval of data

16.1. Storage and retrieval

All data from subjects will be de-identified using subject identification numbers and stored in a controlled environment to ensure confidentiality of the study data. During the course of the study and after its completion, the principal investigator shall provide or allow access to the relevant documents on the collected information of the subjects under conditions of strict confidentiality upon request of the Ministry of Food and Drug Safety (MFDS) or the sponsor.

16.2. Retention and disposal

Data related to the study shall be retained for three years from the time of reporting the results of the study, and all documents shall be disposed of after the retention period according to the following criteria.

1) Electronic files: Permanent deletion by an irreversible means
2) Any recording, print, writing, or other medium of record other than paragraph (1): Shredding or incineration

16.3. Handling of data after discontinuation or withdrawal from a study

Even after subjects withdraw their consent, the anonymously collected data shall be treated in the same manner as the privacy policy for all subjects.

17. Measures to protect the safety of subjects

17.1. Ethical conduct of research

This study will be conducted in accordance with the protocol and in compliance with Good Clinical Practice (ICH-GCP), Good Research Practices, the ethical principles of the Declaration of Helsinki, and other applicable regulations. Standard care (preventive, diagnostic, and therapeutic procedures) remains the responsibility of the physician treating the patient.

17.2. Institutional Review Board (IRB)

The study will begin after the review of the research protocol and consent to use personal information and approval by the IRB of each institution. If changes are made to the study protocol that require IRB approval, the changes will be implemented after receiving approval from the IRB of each institution for review of the revised protocol and privacy agreement (if applicable). Any changes that affect the safety of the subjects will be notified to the IRB as soon as possible for approval.

17.3. Subject consent process

The principal investigator at each institution shall submit the consent form to the respective IRB for review and approval prior to enrollment of subjects and conduct the study with approved consent forms. Written informed consent shall be obtained from each subject and, if necessary, the subject's legal guardian, prior to initiation and enrollment in the research procedures specified in the protocol, and if the subject and legal guardian are illiterate, consent shall be obtained in the presence of an impartial witness. The principal investigator or the person in charge of the research explains the research plan to the research subject and, if necessary, the legal representative of the research subject in sufficient time and obtains a signed informed consent form. Each signature shall be hand-dated by each person signing the consent form, and the original shall be retained by the principal investigator as a record of the clinical study. A copy of the signed consent form shall be provided to the subject or the subject's legal guardian. Also, the process of obtaining consent shall be recorded in the supporting documentation.

17.4. Steering Committee

All endpoints encountered during the study shall be reported to the Steering Committee. The Steering Committee shall review the reported event and make a judgment as to whether it constitutes an efficacy and safety endpoint. Each investigator may be asked to supplement the data to ensure accurate judgment.
The Steering Committee will also meet every six months to review the progress of the study and address any issues that arise. Other occasional meetings may be held at the request of the members as needed. The organization of the Steering Committee is listed in Attachment 2.

18. References

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[Appendix 1] NIHSS (The National Institution of Health Stroke Scale)

INSTRUCTIONS	SCALE DEFINITION	SCORE
1a. Level of Consciousness	0= Alert, 1= Drowsy, 2= Stupor, 3= Coma	
1b. LOC Questions	0= All correct, 1= One correct, 2=Incorrect	
1c. LOC Commands	0= All correct, 1= One correct, 2=Incorrect	
2. Best Gaze	0= Normal, 1= Partial gaze palsy (gaze preference or cranial n palsy), 2= Forced deviation	
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	
4. Facial Palsy	0= normal 1= minor palsy 2= partial palsy 3= complete palsy	
5a. Motor Left Arm	0 = No drift 1 = Drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support 2 = Some effort against gravity, limb cannot get to or maintain (if cue) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity 3 = No effort against gravity, limb falls 4 = No movement 9 = Amputation, joint fusion, explain:	
5b. Motor Right Arm		
6a. Motor Left Leg	0 = No drift 1 = Drift, leg falls by the end of the 5 second period but does not hit bed 2 = Some effort against gravity, leg falls to bed by 5 seconds, but has some effort against gravity 3 = No effort against gravity, leg falls to bed immediately 4 = No movement 9 = Amputation, joint fusion explain:	
6b. Motor Right Leg		
7. Limb Ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs	
8. Sensory	0 = Normal, 1 = partial loss (stupor), 2 = dense loss (nearly complete loss, coma)	
9. Best Language	0 = Normal 1 = mild aphasia (communication possible)	

	2 = severe aphasia 3 = global aphasia (coma)	
10. Dysarthria	0 = Normal 1 = Mild to moderate 2 = Severe 9 = Intubation or other physical barrier	
11. Extinction and inattention (formerly Neglect)	0 = No abnormality 1 = Partial (partial abnormality) 2 = Complete	
Total		

[Appendix 2] mRS (Modified Rankin Scale)

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): ____