Clinical Research Protocol

Triglyceride-lowering therapy with pemafibrate for prevention of atherosclerotic cardiovascular disease in patients with symptomatic intracranial artery stenosis: a multi-center, open-label, randomized controlled trial (PPAR-ICAS)

NCT ID: Not yet assigned

Current Version:
Version 1.0 (October 1, 2025)

Revision History:
Version 1.0 (October 1, 2025)

1. Study Organization

1.1 Principal Investigator (also serves as Coordinating Investigator of the Representative Site) / Representative Site

Name: Kenichi Todo
Institution: Tokyo Women's Medical University Hospital
Department: Department of Neurology
Institution Address: 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
Telephone: 03-3353-8111
Email: todo.kenichi@twmu.ac.jp

1.2 Steering Committee

Name: Takao Hoshino
Institution: Tokyo Women's Medical University Hospital
Department: Department of Neurology

Name: Ryo Itabashi
Institution: Iwate Medical University Hospital
Department: Department of Neurology and Geriatrics

Name: Hiroshi Yamagami
Institution: University of Tsukuba Hospital
Department: Department of Stroke Medicine

Name: Junya Aoki
Institution: Saitama Medical University International Medical Center
Department: Department of Neurology and Stroke Medicine

Name: Yuki Sakamoto
Institution: Nippon Medical School Hospital
Department: Department of Neurology

Name: Kenichiro Sakai
Institution: The Jikei University Hospital
Department: Department of Neurology

Name: Yasuhiro Nishiyama
Institution: University of Fukui Hospital
Department: Department of Neurology

Name: Tomoyuki Ohara
Institution: Kyoto Prefectural University of Medicine Hospital
Department: Department of Neurology

Name: Shuhei Okazaki
Institution: National Hospital Organization Osaka Medical Center
Department: Department of Neurology

Name: Yoshiki Yagita
Institution: Kawasaki Medical School Hospital
Department: Department of Stroke Medicine

Name: Makoto Nakajima
Institution: Kumamoto University Hospital
Department: Department of Neurology

1.3 Protocol Committee
Name: Kenichi Todo
Institution: Tokyo Women's Medical University Hospital
Department: Department of Neurology

Name: Takao Hoshino
Institution: Tokyo Women's Medical University Hospital
Department: Department of Neurology

Name: Satoshi Suda
Institution: Nippon Medical School Hospital
Department: Department of Neurology

Name: Yasuyuki Iguchi
Institution: The Jikei University Hospital
Department: Department of Neurology

Name: Kazumi Kimura
Institution: Kumamoto University Hospital
Department: Department of Neurology

1.4 Imaging Adjudication Committee
Name: Shuji Sakai
Institution: Tokyo Women's Medical University Hospital
Department: Diagnostic Imaging and Nuclear Medicine

Name: Kazufumi Suzuki
Institution: Tokyo Women's Medical University Hospital
Department: Diagnostic Imaging and Nuclear Medicine

1.5 Participating Sites and Site Principal Investigators
See **Appendix 1**.

1.6 Study Office (Contact for Study-related Inquiries)
Contact Person: Takao Hoshino
Institution: Tokyo Women's Medical University Hospital
Department: Department of Neurology
Address: 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
Telephone: 03-3353-8111

Email: hoshino.takao@twmu.ac.jp

1.7 Data Management
Organization: Nexis Co., Ltd.
Responsible Person: Saki Fukuda
Division: Planning Promotion Department

1.8 Monitoring
Organization: Nexis Co., Ltd.
Responsible Person: Saki Fukuda
Division: Planning Promotion Department

1.9 Audit
Organization: Pepro Japan Co., Ltd.
Responsible Person: Tomio Azuma
Division: Clinical Research Promotion Group

1.10 Statistical Analysis
Organization: Tokyo Women's Medical University Hospital
Responsible Person: Yasuhito Sato
Division: Department of Hygiene and Public Health
Position: Part-time Lecturer

1.11 Research and Development Planning Support
Not applicable.

1.12 Coordination and Administrative Management
Organization: Nexis Co., Ltd.
Responsible Person: Yoshiya Hanazawa
Division: Planning Promotion Department

1.13 Persons Sharing the Responsibilities of the Coordinating Investigator
Not applicable.

1.14 Clinical Laboratory Facilities
Clinical laboratory testing will be performed at each participating site.

1.15 Medical and Technical Department/Institution
Name: Tokyo Women's Medical University Hospital
Address: 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

1.16 Contract Research Organization
Name: Nexis Co., Ltd.
Address: 3-7-27-1 Minoshima, Hakata-ku, Fukuoka 812-0017, Japan
Contracted Duties: data management, monitoring, and safety information management

Oversight: Tokyo Women's Medical University Hospital will supervise the contracted duties through routine operations, receipt of reports from the contractor, and appropriate oversight and instruction.

1.17 Efficacy and Safety Evaluation Committee
Not established.

2. Background
2.1 Target Disease
Symptomatic intracranial arterial stenosis with hypertriglyceridemia (triglycerides [TG]).

2.2 Current Status of the Target Disease, Standard Therapy, Treatment Outcomes, and Unmet Needs
At present, the only lipid-lowering therapy with established evidence for secondary prevention after ischemic stroke or transient ischemic attack (TIA) is low-density lipoprotein cholesterol (LDL-C)-lowering therapy with statins.[1] However, the reduction in recurrent vascular risk achieved by LDL-C lowering is approximately 20%,[2] which is insufficient. Reducing residual vascular risk after LDL-C lowering therefore remains an important challenge.

In recent years, TG has attracted attention as a strongly atherogenic factor and a potential new therapeutic target in vascular disease[3]. Large-scale epidemiologic studies have shown that hypertriglyceridemia is an independent risk factor for future cardiovascular disease.[3] We have further reported that hypertriglyceridemia is (1) more common in Japanese and Asian patients with ischemic stroke than in Western populations, (2) strongly associated with intracranial atherosclerotic stenosis, and (3) associated with an approximately twofold increase in recurrent vascular risk after ischemic stroke regardless of statin use.[4]

Ischemic stroke or TIA due to intracranial atherosclerotic stenosis (symptomatic intracranial arterial stenosis) is known to be more common in Japanese and Asian populations than in Western populations, and carries an annual recurrence risk exceeding 10%, indicating a poor prognosis.[5] The usefulness of stenting has been denied in multiple randomized controlled trials,[6,7] and at present no established therapy exists other than antiplatelet therapy and statins. New treatment strategies are therefore needed.

Given that hypertriglyceridemia is common in Japanese and Asian patients with ischemic stroke and is particularly strongly associated with intracranial arterial stenosis, TG-lowering therapy may become a new therapeutic option to add to statin therapy. However, few high-quality studies have evaluated TG-lowering therapy in patients with ischemic stroke or TIA. In addition, because racial differences are substantial in both stroke and lipid metabolism, validation in Japanese and Asian populations is necessary.

2.3 Information on Investigational Medical Products to Be Used in the Study (Investigational Product / Control Product: Package Insert Information, etc.)
2.3.1 Name (generic and brand name) and overview
Generic name: Pemafibrate
Brand names: Parmodia XR Tablets 0.2 mg / 0.4 mg; Parmodia Tablets 0.1 mg

Approval numbers: 35000AMX00127 (Parmodia XR 0.2 mg), 35000AMX00128 (Parmodia XR 0.4 mg), 22900AMX00581 (Parmodia 0.1 mg)
Marketing authorization holder: Kowa Company, Ltd.
Approved indication: Hyperlipidemia (including familial forms)
Dosage form: pale yellow, round, film-coated tablet (Parmodia XR 0.2 mg / 0.4 mg); white, round, scored, film-coated tablet (Parmodia 0.1 mg)
Storage: room temperature

2.3.2 Route of administration, dosage, and treatment period
Route of administration: oral
Dosage: Parmodia XR 0.2 mg, one tablet once daily; or Parmodia 0.1 mg, one tablet twice daily. The dose may be adjusted according to age, comorbidities, and TG level in accordance with the package insert.
The maximum dose is 0.4 mg/day.
Treatment period: 1 year.

2.3.3 Target population (age, sex, disease)
Men and women aged 18 years or older with symptomatic intracranial arterial stenosis and concomitant hypertriglyceridemia.

2.3.4 Clinically important findings from nonclinical studies and other clinical studies
Historically, fibrates have been used to treat hypertriglyceridemia. Randomized controlled trials and subanalyses in patients with coronary artery disease or diabetes have reported significant reductions in cardiovascular event risk with fibrates.[8] However, concerns regarding adverse effects such as rhabdomyolysis and renal impairment limited their clinical use because concomitant use with statins was generally contraindicated.

Against this background, pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) that can be used together with statins, was approved in Japan in 2018 ahead of the rest of the world. Like conventional fibrates, it activates PPARα, but its modified chemical structure confers stronger TG-lowering effects and fewer adverse effects.[9] The PROMINENT trial, the only event-driven outcome trial of pemafibrate, enrolled patients with type 2 diabetes, most of whom were Western, and did not demonstrate a reduction in major cardiovascular events.[10] In contrast, in our single-center study in Japanese patients with chronic ischemic stroke, 2 years of pemafibrate treatment lowered serum TG, increased HDL cholesterol, reduced inflammatory markers (high-sensitivity CRP and IL-6), and was associated with less progression of intracranial arterial stenosis than reported in previous studies.[11]

3. Objective
The objective of this study is to evaluate whether pemafibrate treatment prevents progression of intracranial arterial stenotic lesions in patients with symptomatic intracranial arterial stenosis and hypertriglyceridemia.

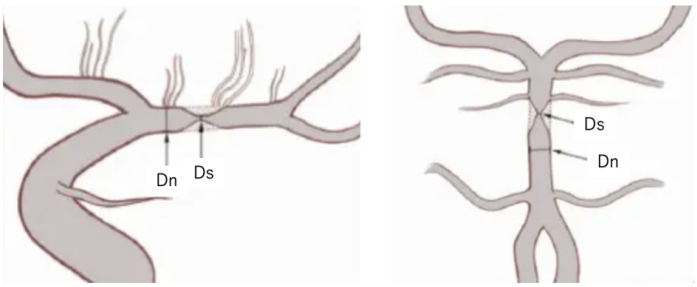
4. Inclusion and Exclusion Criteria for Study Participants
4.1 Inclusion Criteria
1. Clinically stable ischemic stroke or high-risk TIA ($ABCD^2$ score >=4) between 24 hours and 3 years from onset at enrollment.

2. Contrast-enhanced CT angiography (CTA) within 3 months prior to consent demonstrating 50-99% stenosis (WASID criteria[12]) in a symptomatic intracranial artery: intracranial internal carotid artery, middle cerebral artery (M1/M2), anterior cerebral artery (A1), vertebral artery (V4), basilar artery, or posterior cerebral artery (P1).
3. Fasting triglycerides (TG) 150-499 mg/dL, or non-fasting TG 175-499 mg/dL, measured within 4 weeks prior to consent.
4. Men or women aged >=18 years at the time of consent.
5. Ability to obtain written informed consent from the patient or a legally authorized representative.

Rationale

1. The study includes patients with ischemic stroke or TIA and allows not only acute cases but also chronic cases within 3 years after onset. However, enrollment of early cases within 1 month after onset will be encouraged because such lesions are considered unstable and most likely to benefit from treatment. Percent stenosis will be measured by the WASID method using the formula: stenosis (%) = (1 - Ds/Dn) x 100 (**Figure 1**).[12] The $ABCD^2$ score is a scoring system that stratifies stroke recurrence risk after TIA according to the sum of component scores (**Table 1**).[13] Current guidelines consider TIA with an $ABCD^2$ score of 4 or higher to be high risk and recommend inpatient management.[1]
2. Imaging tests for intracranial arterial stenosis generally include catheter angiography, contrast-enhanced CTA, and MRA. MRA is simple and less invasive but has lower spatial resolution and may overestimate stenosis. Catheter angiography has high resolution but is invasive and impractical for consecutive enrollment. CTA therefore provides the best balance between invasiveness and image resolution for this study.
3. The TG cutoff values are based on guideline recommendations: fasting TG >=150 mg/dL or non-fasting TG >=175 mg/dL.[14] In our cohort of patients with ischemic stroke, TG >=150 mg/dL was also significantly associated with stroke risk.[4] Marked hypertriglyceridemia (TG >=500 mg/dL) is excluded because prompt therapeutic intervention is considered necessary owing to the risk of acute pancreatitis.
4. The lower age limit is 18 years, the legal age of adulthood.
5. Only patients for whom written informed consent can be confirmed will be enrolled. Because some patients with ischemic stroke may have aphasia or motor impairment, enrollment based on consent from a legally authorized representative is also permitted in accordance with the procedures described below.

Figure 1. WASID method



Stenosis (%) = (1 - Ds/Dn) x 100.

Table 1. ABCD^2 score

Component	Criteria	Score
Age	Age ≥60 years	1
Blood pressure	Systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg	1
Clinical features	Unilateral weakness	2
	Speech impairment without weakness	1
Duration of symptoms	≥60 minutes	2
	10–59 minutes	1
Diabetes	Diabetes mellitus	1
Total		0–7

4.2 Exclusion Criteria

1. Patients with intracranial arterial stenosis due to non-atherosclerotic disorders (e.g., vasculitis, moyamoya disease, intracranial arterial dissection).
2. Patients with >=70% stenosis of the extracranial carotid artery (NASCET criteria[15]).
3. Patients with neurological deterioration within 24 hours prior to enrollment.
4. Patients who received intravenous thrombolysis or mechanical thrombectomy within 24 hours prior to enrollment.
5. Patients scheduled to undergo revascularization procedures (percutaneous transluminal angioplasty, stent placement, carotid endarterectomy, or cerebral bypass surgery).
6. Patients who meet any contraindication to pemafibrate, including: (1) history of hypersensitivity to pemafibrate; (2) severe hepatic impairment or liver cirrhosis classified as Child-Pugh B or C; (3) cholelithiasis; (4) pregnancy or suspected pregnancy; (5) concomitant use of cyclosporine or rifampin.
7. Patients who have taken pemafibrate or any fibrate within 12 weeks prior to consent.
8. Patients with contraindications to iodinated contrast media.
9. Patients on dialysis.
10. Patients with a history of pancreatitis attributable to hypertriglyceridemia.
11. Patients with severe systemic comorbidities with an expected survival <12 months.
12. Patients who may be pregnant, are pregnant, or are breastfeeding.
13. Any other condition for which the principal or sub-investigator judges participation to be inappropriate.

Rationale

1. Patients with stenotic lesions caused by non-atherosclerotic disorders are excluded.
2. Patients with severe extracranial carotid stenosis are excluded because reduced cerebral perfusion may make accurate evaluation of intracranial arterial stenosis difficult.
3. Patients with unstable neurologic symptoms are not enrolled because accurate assessment of the study drug effect would be difficult.
4. Patients immediately after intravenous thrombolysis or mechanical thrombectomy are not enrolled because accurate assessment of the study drug effect would be difficult. Enrollment is permitted if at least 24 hours have elapsed after such treatment.
5. Patients undergoing revascularization are excluded because the study drug effect may be overestimated and peri-procedural stroke may occur.
6. Patients who meet contraindications to the study drug are excluded.

7. Patients already receiving the study drug are excluded.
8. Patients who cannot undergo contrast-enhanced imaging are excluded because intracranial arterial evaluation would not be possible.
9. Patients on dialysis are excluded in consideration of the risk of adverse reactions to the study drug.
10. Patients with a history of pancreatitis due to hypertriglyceridemia are excluded because withholding TG-lowering therapy may increase pancreatitis risk.
11. Patients expected to be difficult to follow are excluded.
12. Pregnant or breastfeeding patients are excluded.
13. Patients judged inappropriate for study participation by the investigator are excluded.

4.3 Participant-specific Discontinuation Criteria

1. The participant requests withdrawal of consent.
2. Compliance with the study protocol becomes impossible.
3. The study as a whole is discontinued.
4. The participant becomes pregnant.
5. During follow-up, TG rises markedly and hypertriglyceridemia-related complications (such as acute pancreatitis) are considered likely or suspected, or the treating physician judges that initiation or intensification of pharmacologic therapy for hypertriglyceridemia (including pemafibrate) is required for participant safety.
6. The principal investigator or sub-investigator judges that continuation in the study is difficult for any other reason.

5. Study Design and Methods

5.1 Type of Clinical Study

Open-label, randomized, parallel-group controlled trial.

5.2 Randomization and Blinding

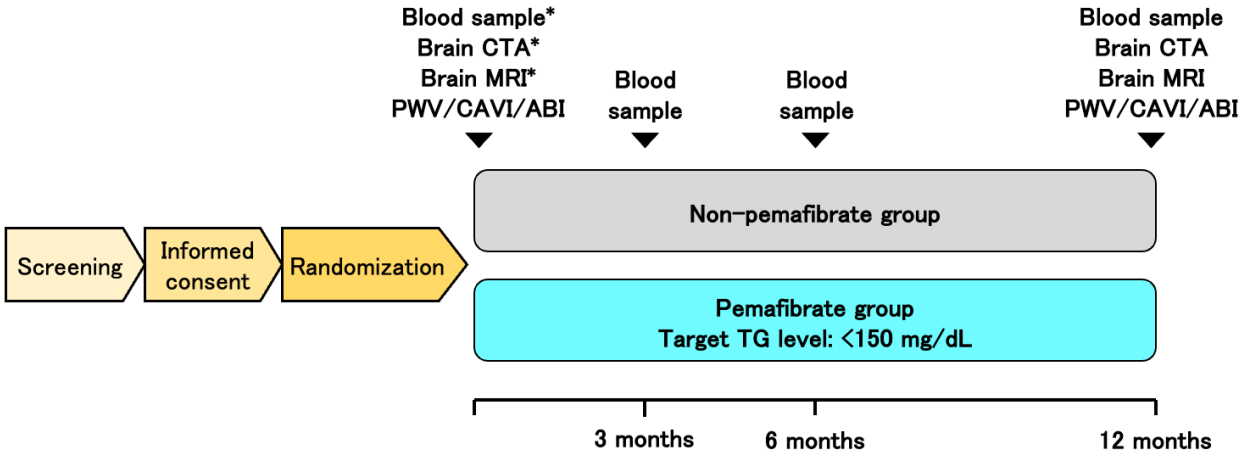
Participants will be allocated 1:1 to the intervention group or control group using dynamic allocation balancing the following factors specified in advance: age (<75 / >=75 years), intracranial arterial stenosis severity (moderate, 50-69% / severe, 70-99%), and time from TIA or ischemic stroke onset (<1 month / >=1 month). Randomization will be performed on a computer managed by the study office according to a pre-generated randomization code, and the allocation result will be communicated immediately to the treating physician. The treating physician, relevant staff, and participant will know the assigned group.

6. Use of Drugs / Medical Devices in Study Participants

6.1 Treatment and Observation Periods (including follow-up)

As shown in **Figure 2**, both the treatment period and the observation period are set at 1 year from registration. Participants will be assigned to either the non-pemafibrate group or the pemafibrate group. Participants assigned to pemafibrate will receive oral pemafibrate 0.2 mg/day according to the package insert (once daily when using Parmodia XR; twice daily when using Parmodia). The target TG level is <150 mg/dL, and dose escalation up to 0.4 mg/day may be considered according to TG levels. However, when eGFR is <30 mL/min/1.73 m2, the maximum dose is 0.2 mg/day.

Figure 2. Study schedule



* Results of the screening tests can be used for registration.

- Both groups will receive antithrombotic therapy and risk factor management (blood pressure, LDL-C, diabetes, and smoking) based on the stroke guidelines.
- LDL-lowering therapy with statins, ezetimibe, and PCSK-9 inhibitors is permitted during the study period.
- TG-lowering therapy with fibrates and omega-3 fatty acid preparations is prohibited during the study period.

6.2 Detailed Procedures (including schedule)

Registration, randomization, and follow-up will be conducted according to the study schedule below (**Table 2**). At registration (Day 1), demographic characteristics (age, sex, race), background and medical history (past history, current illness, medication history, lifestyle history, personal habits, allergy history), physical findings (height and weight), vital signs (blood pressure and pulse rate), neurologic findings, blood tests, head CTA, brain MRI/MRA, ankle brachial index (ABI), cardio ankle vascular index (CAVI), pulse wave velocity (PWV), medication adherence, concomitant medications, vascular events, adverse events, and activities of daily living using the modified Rankin Scale (mRS: **Table 3**) will be assessed. After randomization and study treatment initiation, physical findings, vital signs, neurologic findings, blood tests, medication adherence, concomitant medications, vascular events, and adverse events will be assessed at Day 90 and Day 180. At 1-year follow-up (Day 365), these assessments will be repeated together with head CTA, brain MRI/MRA, ABI/CAVI/PWV, and mRS. The follow-up period is 1 year.

Table 2. Study Schedule

Period	Chart Screening	Visit 1 Day 1 Registration	Visit 2 Day 90 / 3 months (+/- 30 days)	Visit 3 Day 180 / 6 months (+/- 30 days)	Visit 4 Day 365 / 12 months (+/- 60 days)
Informed consent		X			
Demographic characteristics	X	X			
Background / medical history	X	X			
Physical findings	X	X	X	X	X
Vital signs	X	X	X	X	X
Neurologic findings	X	X	X	X	X
Blood tests	X*	X†	X†	X†	X†
Head CTA‡	X	X‖			X
Brain MRI/MRA§		X‖			X#
ABI / CAVI / PWV		X‖			X
Randomization / allocation		X			
Study treatment		X	X	X	X
Medication adherence		X	X	X	X
Concomitant medications		X	X	X	X
Vascular events		X	→	→	→
Adverse events		X	→	→	→
mRS		X			X
Case report form entry		X	X	X	X

* At screening, the TG value may be either fasting (150-499 mg/dL) or non-fasting (175-499 mg/dL), but the registration value must be fasting. If fasting blood sampling was already performed at screening, repeat testing at registration is not necessarily required. Values measured within 4 weeks before consent may be used at registration.

† WBC (including neutrophil and lymphocyte percentages), RBC, hemoglobin, hematocrit, platelets, fasting TG, HDL-C, LDL-C, fasting glucose, HbA1c, AST, ALT, gamma-GTP, creatinine, eGFR, CK, CRP, PT-INR, APTT, fibrinogen, and D-dimer. Items collected only at sites that measure them in routine practice: RLP-C, apolipoprotein C-III, lipoprotein(a), high-sensitivity CRP, IL-6, and total homocysteine.

‡ Head CTA acquisition conditions must satisfy the following at both registration and Day 365: helical acquisition is recommended (volume acquisition acceptable); detector rows >=64; beam pitch <1.0; scan timing not specified; tube voltage >=100 kV (to help distinguish calcification from high-concentration contrast material); contrast injection rate >=23 mgI/kg/s by fractional dose; contrast injection duration >=12 seconds (>=10 seconds for volume acquisition); reconstruction method not specified; reconstructed slice thickness <1 mm; reconstruction interval <1 mm.

§ Brain MRI/MRA must include diffusion-weighted imaging, T1-weighted imaging, T2-weighted imaging, FLAIR, T2*-weighted imaging or SWI, and TOF-MRA. At registration and Day 365, the same field strength (1.5T or 3.0T) should be used, and the same scanner should be used whenever possible.
|| Examinations performed within 3 months before consent may be used as registration data, provided that they were performed after the TIA or ischemic stroke onset. If they were performed at screening, repeat testing at registration is not required.
Not mandatory; performed when clinically indicated.

Table 3. modified Rankin Scale

Score	Description
0	No symptoms
1	No significant disability despite symptoms
2	Slight disability (unable to carry out all previous activities, but able to look after own affairs without assistance)
3	Moderate disability (requires 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	Death

6.3 Treatments Permitted Before and During the Study (including emergency treatment)

Standard treatments recommended in the 2021 Japanese Guidelines for the Management of Stroke are permitted. LDL-lowering therapy with statins, ezetimibe, and PCSK9 inhibitors is allowed. If omega-3 fatty acid preparations (icosapent ethyl or docosahexaenoic acid ethyl ester) were already being taken before study entry, continuation at the same or a reduced dose during the study is permitted; dose escalation is not permitted.

6.4 Treatments Prohibited Before and During the Study

TG-lowering therapy with fibrates is prohibited before and during the study. For patients not already receiving omega-3 fatty acid preparations (icosapent ethyl or docosahexaenoic acid ethyl ester) before study entry, initiation of these drugs during the study is prohibited.

6.5 Procedures for Confirming Compliance

Ongoing compliance with allocation and with required examinations specified in the protocol will be confirmed in both study arms. Under the direction of the site principal investigator, sub-investigators will verify compliance at each visit using source documents (prescription orders, dispensing records, laboratory reports, medical records, etc.) and record the results in the eCRF.

In the intervention group, adherence to study treatment will be assessed at each visit by cross-checking prescription/dispensing records (including medication notebooks when available), interviews regarding dosing schedule, reasons for missed doses, and adverse effects, together with referral letters or records from other institutions; pill counts may be used as needed. If the adherence rate is low (as a guide, <80%), the reasons for poor adherence will be explored and adherence support measures will be implemented. Dose changes, temporary interruption, or

permanent discontinuation will be documented in source records and the eCRF, together with the medical reasons, duration, and whether treatment was restarted.

In the control group, prescription/dispensing records and information from other institutions will be checked at each visit to confirm that pemafibrate has not been newly started during follow-up. If crossover treatment is identified, it will be evaluated as a major protocol deviation and the reason, start date, and duration will be recorded.

In both groups, concomitant medication changes will be reviewed at every visit, with particular attention to prohibited drugs, addition or switching within the same drug class, and new use of drugs with potential interactions.

The required examinations listed in Section 6.2 must be performed at the specified time points and within the allowed windows and conditions (e.g., fasting blood sampling). Approximately 1 month before each scheduled follow-up, email reminders for visits and tests will be sent to site investigators and sub-investigators. If an examination is missed or performed under unacceptable conditions (e.g., non-fasting), it will be documented as a deviation with the reason and impact, and supplementary testing will be arranged as promptly as possible whenever feasible.

6.6 Drug Management Procedures

No placebo will be used in this study, and only already approved, commercially available drugs will be used. Because the study is open-label, no special drug accountability procedures beyond ordinary clinical management will be implemented.

7. Endpoints

7.1 Primary Endpoint

- Progression in intracranial arterial stenosis on CTA at 12 months from enrollment (progression vs. no progression [no change or improvement]).

Stenosis is assessed by the WASID method[12]; progression is defined as an absolute increase of >=10 percentage points in percent stenosis or the development of occlusion, stability as a change of <10 percentage points in either direction, and improvement as an absolute decrease of >=10 percentage points. For example, a lesion with 50% stenosis at baseline will be considered to have progressed if it worsens to >=60%, and a lesion with >=90% stenosis at baseline will be considered to have progressed if it becomes 100% occluded. Percent stenosis will be measured centrally using automated analysis software (Aquarius iNtuition Viewer; Terarecon, Durham, NC). Head CTA interpretation and stenosis measurement will be performed, with treatment allocation masked, by two independent expert readers (e.g., neurologists or radiologists) who are not involved in clinical care at the participating sites. If the two readers disagree regarding progression, no change, or improvement, the final judgment will be reached by consensus or, when necessary, adjudication by a third evaluator. Representative cases and an evaluation manual will be shared before evaluation begins to standardize assessment criteria.

7.2 Key Secondary Endpoints (supplementary analyses of the primary endpoint)

- Change in intracranial arterial stenosis on CTA at 12 months from enrollment (three categories: progression, no change, improvement).

- Improvement in intracranial arterial stenosis on CTA at 12 months from enrollment (improvement vs. no improvement [progression or no change]).

In this study, secondary endpoints that are considered most important after the primary endpoint are defined prospectively as key secondary endpoints. These correspond to supplementary analyses intended to aid interpretation of the primary endpoint. Because both key secondary endpoints directly capture change in intracranial arterial stenosis itself, they are positioned separately from other secondary endpoints as outcomes that are particularly relevant to mechanistic understanding and interpretation of the study results.

7.3 Other Secondary Endpoints

- Change in percent stenosis by the WASID method.
- Proportion of intracranial arterial stenosis progression/improvement per the TOSS[16] and TOSS-2[17] criteria (**Table 4**).
- Proportion of intracranial arterial stenosis progression/improvement per the Wong KS criteria (**Table 5**)[18].
- Major cardiovascular events (MACE): the following individual events and their composite: ischemic stroke (fatal, nonfatal), TIA, intracranial hemorrhage (fatal, nonfatal), any stroke (ischemic stroke, TIA, intracranial hemorrhage), myocardial infarction (fatal, nonfatal), any coronary artery disease event (myocardial infarction or angina treated with PCI or CABG), symptomatic peripheral artery disease (with intermittent claudication, ulceration, or gangrene, or requiring revascularization), vascular death, and all-cause mortality.
- Activities of daily living by mRS score (mRS 0-1, 0-2, and 0-3 proportions, and the overall mRS score distribution).
- Changes in cerebral small vessel disease on brain MRI (Fazekas scale, cerebral microbleeds, total SVD score).
- Changes in ABI, CAVI, and PWV.
- Changes in blood biomarkers: complete blood count; fasting TG, HDL-C, LDL-C, RLP-C; apolipoprotein C-III; lipoprotein(a); fasting plasma glucose; HbA1c; AST, ALT, gamma-GTP; creatinine, eGFR; CK; CRP, high-sensitivity CRP; IL-6; total homocysteine; PT-INR; APTT; fibrinogen; D-dimer.
- Safety: occurrence of adverse events and illnesses.

Table 4. TOSS / TOSS-2 Grading Criteria

Grade	Finding
1	Normal
2	Mild (<50% stenosis)
3	Moderate (>=50% stenosis)
4	Severe (loss of flow signal at the stenotic segment, with preserved distal flow signal)
5	Occlusion (complete loss of flow signal)

An increase of at least one grade is defined as progression, and a decrease in grade is defined as improvement.

Table 5. Wong KS Grading Criteria

Grade	Finding
1	Normal or 0-29% stenosis

2	30-69% stenosis
3	70-99% stenosis
4	Occlusion

An increase of at least one grade is defined as progression, and a decrease in grade is defined as improvement.

8. Statistical Considerations

8.1 Analysis Sets

8.1.1 Full Analysis Set (FAS)

The FAS will consist of all registered participants except ineligible cases, untreated cases, and participants with no post-treatment data for efficacy endpoints.

8.1.2 Per Protocol Set (PPS)

The PPS will consist of FAS participants excluding those with major protocol noncompliance or discontinuation.

8.1.3 Safety Analysis Set

The safety analysis set will consist of all registered participants except untreated cases.

8.2 Target Sample Size and Rationale

Target sample size: 270 participants.

The hypothesis to be tested is that the novel TG-lowering drug pemafibrate prevents progression of intracranial arterial stenosis. Akins et al., using digital subtraction angiography, reported >=10% progression in stenosis in 40% of cases over 26.7 months.[19] In the TOSS trial using MRA, progression defined by a rough five-grade classification (normal, mild, moderate, severe, occlusion) occurred in 29% of placebo-treated patients over 6 months.[16] In the similarly designed TOSS-2 trial, progression occurred in 16% of patients in the clopidogrel group over 7 months.[17] In our own MRA-based study, progression of intracranial arterial stenosis in pemafibrate-treated patients was 8.3% over 2 years, roughly half the rate reported previously.[11] Because CTA, which will be used in this study, allows more accurate measurement than MRA, more patients may be classified as having progression than in previous reports. Based on prior reports and our clinical experience, the progression rate in the non-pemafibrate group is expected to be >=30% per year. We therefore assumed a progression rate of 30% per year in the control group and that pemafibrate would reduce this by 50% to 15% per year.

With a two-sided α of 0.05 and a power of 0.8, the required sample size is 121 participants per group (242 total). Allowing for dropout, the study will enroll 270 participants (135 per group).

8.3 Criteria for Early Discontinuation of the Study

1. Recruitment is difficult and the target sample size is judged unattainable.
2. The study objective has been achieved before the planned sample size or study period is reached.
3. Continuation of the study is judged to provide no benefit.
4. An unpredictable serious adverse event with a causal relationship that cannot be ruled out occurs.
5. The certified review board or the Minister of Health, Labour and Welfare requests discontinuation.

6. A major violation of the study has been identified.

8.3.1 Examinations or Other Procedures That Impose Significant Burden, and Outline of Medical Products

Not applicable.

8.4 Handling of Cases

In principle, handling of registered cases will be determined by discussion among the coordinating investigator, the statistical analysis lead, and others as appropriate. If new issues arise, case handling will likewise be determined through discussion, and the decision will be documented.

8.5 Data Handling

If questions arise during data tabulation or analysis, the coordinating investigator and the statistical analysis lead will determine the appropriate handling. If missing data exist for primary or secondary endpoints, the occurrence and reasons for missingness will be classified and recorded, and appropriate methods for imputation or exclusion will be specified. Details, including the handling of outliers and abnormal values, will be defined in the statistical analysis plan. Conducted analyses will be summarized in the analysis report.

8.6 Statistical Analysis Items and Plan

All analyses will be performed after study treatment is completed for all participants and the database is locked. For all efficacy endpoints, the primary analyses will use the FAS, with PPS analyses performed as supportive analyses. Safety analyses will use the safety analysis set. Detailed statistical methods will be specified in a statistical analysis plan prepared before database lock. The significance level for all statistical analyses will be two-sided 5%.

8.6.1 Analysis of Participant Characteristics

Categorical, continuous, and ordinal variables will be summarized using appropriate statistics (frequencies, means, standard deviations, medians, interquartile ranges, minima, and maxima) and compared between groups using chi-square tests, Fisher exact tests, unpaired t-tests, or Wilcoxon rank-sum tests, as appropriate.

8.6.2 Analysis of the Primary and Key Secondary Endpoints

For the primary endpoint (presence or absence of progression of intracranial arterial stenosis) and the key secondary endpoint (presence or absence of improvement), group proportions will be compared using the chi-square test or, when appropriate, Fisher exact test, and odds ratios with 95% confidence intervals will be estimated using logistic regression models. The key secondary endpoint of three-level change in intracranial arterial stenosis (progression / no change / improvement) will be compared using the chi-square test, and a common odds ratio with 95% confidence interval will be estimated using an ordinal logistic regression model (shift analysis). In all models, allocation factors and clinically important baseline factors may be included as covariates to provide covariate-adjusted estimates. Cases undergoing unplanned revascularization during follow-up will be handled as "progression" according to the prespecified endpoint definition.

8.6.3 Analysis of Other Secondary Endpoints
Appropriate statistical methods will be applied according to the data type. Continuous variables will be compared between groups using t-tests, Wilcoxon rank-sum tests, ANCOVA, or other methods, with baseline adjustment when appropriate. Change in intracranial arterial stenosis (progression / no change / improvement) will be analyzed using chi-square tests, Mantel-Haenszel tests, or ordinal logistic regression (shift analysis). For mRS, distributional comparison (Wilcoxon), shift analysis, and supplementary binary analyses will be performed. Event outcomes will be analyzed using chi-square or Fisher exact tests; time-to-event outcomes will be analyzed using Kaplan-Meier methods and Cox proportional hazards models. Exploratory analyses will visualize TG changes and stenosis changes using waterfall plots and will assess correlations between TG change rate, stenosis change rate, and other clinical indices using Pearson or Spearman correlation coefficients. Within-subject before/after comparisons will use paired t-tests or Wilcoxon signed-rank tests for continuous variables and McNemar or Bowker tests for categorical variables.

8.6.4 Analysis of Safety Endpoints
Deaths and adverse drug reactions will be evaluated using chi-square tests and, where appropriate, Kaplan-Meier curves with log-rank tests.

8.6.5 Interim Analysis
No interim analysis is planned.

8.6.6 Procedures for Changes to the Original Analysis Plan
If changes are made to the original statistical analysis plan, the protocol or statistical analysis plan will be revised and the change will also be described in the final study report.

8.7 Final Analysis
Analyses will be performed after all available case data have been fixed. The statistical analysis lead will prepare an analysis report and submit it to the coordinating investigator.

9. Adverse Events / Illnesses
9.1 Procedures for Collection, Recording, and Reporting of Illness Information
Investigators will record all adverse events occurring in study participants during study participation and assess their causal relationship to the study. Definitions, assessment methods, reportable events, and reporting timelines for adverse events and illnesses will follow the separate procedure manual, "Procedures for Handling Adverse Events and Illnesses." In this study, adverse events occurring from the start of treatment until 1 month after completion of protocol treatment will be collected.

When an event occurs, the site principal investigator at the participating institution where the event occurred will report it to the head of that institution and to the coordinating investigator in accordance with the procedure manual. The coordinating investigator will report illnesses to the certified review board (CRB) and the Minister of Health, Labour and Welfare as required by law and by the procedure manual. The CRB for this study is the JIHS Certified Clinical Research Review Board. The coordinating investigator will notify site investigators of CRB opinions and, when necessary, provide safety information to Kowa Company, Ltd., the manufacturer and distributor of the study drug.

9.1.1 Reporting of Illnesses to the Certified Clinical Research Review Board (for studies not using unapproved or off-label medical products)

The scope and timelines for reporting illnesses to the CRB and the Minister of Health, Labour and Welfare are specified in the separate procedure manual, in the section "Scope and Timelines for Reporting Illnesses and Adverse Events in Specified Clinical Research."

9.2 Observation Period After Occurrence of an Illness

After an illness occurs, investigators will observe the participant as far as possible until the illness resolves or improves. However, if the participant is judged, on medical grounds, unlikely to recover completely, study-specific observation may be ended after explanation to the participant, although treatment for that condition will be continued as far as possible.

10. Direct Access to Source Documents

The coordinating investigator will ensure, in the protocol or other written agreement, that the site investigators and participating institutions permit direct access to all clinical study-related records for monitoring, auditing, and inspection by the certified review board and regulatory authorities.

For this study, the following will be treated as source documents:
- Medical records (including charts, nursing records, and worksheets)
- Consent forms
- Data entered directly into the EDC system or case report forms
- Other documents used to complete the case report forms

11. Quality Control and Quality Assurance

11.1 Monitoring Methods

The coordinating investigator will prepare a monitoring procedure manual for this protocol and ensure that monitoring is conducted in accordance with that manual and the protocol. Persons engaged in the clinical study will not monitor duties that they directly perform. Monitoring personnel will report monitoring results to the coordinating investigator. Site investigators will notify the coordinating investigator of monitoring findings as necessary, and the coordinating investigator will share relevant information with the other site investigators.

11.2 Audit Methods (if conducted)

The coordinating investigator will prepare an audit procedure manual for this protocol and ensure that audits are conducted in accordance with that manual and the protocol. Persons engaged in the clinical study, and those engaged in monitoring of that study, will not perform the audit. Audit personnel will report audit results to the coordinating investigator. Site investigators will notify the coordinating investigator of audit findings as necessary, and the coordinating investigator will share relevant information with the other site investigators.

12. Ethical Considerations

12.1 Compliance with Laws, Regulations, and Guidelines

This study will be conducted in compliance with the ethical principles of the Declaration of Helsinki, the Clinical Trials Act, related notifications, and this protocol. The materials required by law, including the protocol and implementation plan, will be reviewed and approved by the certified clinical research review board. Thereafter, each site investigator will obtain permission

from the head of the participating institution and complete registration in jRCT before starting the study. The same procedures will be followed before implementing any changes to these materials. Each site investigator will ensure that all personnel involved in the study at the site, including the investigator, have completed education and training in research ethics and other necessary knowledge and skills, and continue to receive training throughout the study period.

12.2 Expected Benefits and Burdens to Participants, Foreseeable Disadvantages, and Measures to Minimize Burden and Disadvantage

Participation in this study does not directly guarantee benefit to the participant. Participants assigned to the pemafibrate group may experience reduced progression of atherosclerotic lesions and reduced recurrence of ischemic stroke compared with the non-pemafibrate group. If the results of this study can be generalized to the wider stroke population, they may contribute to future advances in stroke care.

Pemafibrate is already an approved lipid-lowering drug, but adverse reactions listed in the package insert may occur. Major and other adverse reactions from the August 2024 package inserts for Parmodia 0.1 mg (2nd edition) and Parmodia XR 0.2 mg (5th edition) are summarized below. Expected adverse reactions should be confirmed against the most recent package insert.

Parmodia 0.1 mg tablets

(1) Major adverse reactions

- Rhabdomyolysis (frequency unknown): characterized by myalgia, weakness, CK elevation, and increases in blood and urinary myoglobin, and may be accompanied by severe renal impairment including acute kidney injury. If this occurs, treatment must be stopped immediately and appropriate measures taken.
- Hepatic dysfunction and jaundice (frequency unknown).

(2) Other adverse reactions

Category	**>=1%**	**0.1 to <1%**
Hepatic	Cholelithiasis	Abnormal liver function, increased AST, increased ALT
Musculoskeletal		Increased CK, increased blood myoglobin, myalgia
Skin		Rash, pruritus
Other	Diabetes mellitus (including worsening)	Increased glycohemoglobin, increased LDL, increased uric acid in blood

Parmodia XR tablets

(1) Major adverse reactions

- Rhabdomyolysis (frequency unknown): characterized by myalgia, weakness, CK elevation, and increases in blood and urinary myoglobin, and may be accompanied by severe renal impairment including acute kidney injury. If this occurs, treatment must be stopped immediately and appropriate measures taken.
- Hepatic dysfunction and jaundice (frequency unknown).

(2) Other adverse reactions

Category	>=0.5%	0.1 to <0.5%	Frequency unknown
Hepatic	Increased ALT		Cholelithiasis, abnormal liver function, increased AST
Musculoskeletal	Increased CK, myalgia		Increased blood myoglobin
Skin	Rash		Pruritus
Other		Diabetes mellitus (including worsening)	Increased glycohemoglobin, increased LDL, increased uric acid in blood

If any adverse reaction occurs, the site principal investigator and sub-investigators will provide appropriate management and the best available treatment.

For participants allocated to the non-pemafibrate group, initiation of new TG-lowering therapy will in principle not occur during the observation period. However, if TG rises markedly during follow-up and complications related to hypertriglyceridemia (such as acute pancreatitis) are suspected, or if the treating physician judges that starting pharmacologic therapy for hypertriglyceridemia is necessary for participant safety, the participant will be withdrawn from the study and switched to ordinary treatment including pemafibrate.

12.3 Handling of Research Results (including incidental findings) in the event that important findings relevant to the participant's health or inherited genetic characteristics may be obtained

12.3.1 If the participant wishes to receive explanations regarding genetic findings or other results obtained through this study, the investigator will in principle provide such explanation, taking into account: (1) the precision and certainty of the findings as information for evaluating the participant's health status; (2) whether the findings constitute an important fact for the participant's health; and (3) whether explaining the findings could seriously interfere with the proper conduct of the research.

12.3.2 The investigator will respect the wishes of a participant who, after being informed of the policy for explanation of study results, does not wish to receive an explanation. However, even when the participant does not wish to receive such explanation, if the results are found to have a serious impact on the life of the participant or blood relatives and an effective means of response exists, the investigator will seek the opinion of the ethics committee regarding whether and how to provide an explanation, taking into account: (1) the impact on the life of the participant and relatives; (2) the existence of effective treatment and the participant's health status; (3) the possibility that relatives may have the same disease; and (4) what was explained at the time of informed consent regarding disclosure of study results.

12.3.3 Based on the ethics review under Section 12.3.2, the investigator will provide sufficient explanation to the participant or others concerned, confirm the participant's wishes, and will not provide an explanation if the participant still does not wish to receive one.

12.3.4 Without the participant's consent, study results obtained from the participant will not in principle be explained to anyone other than the participant. However, when a legally authorized representative or blood relative requests an explanation, the investigator may provide one after considering the reason and necessity for the request and obtaining the opinion of the ethics committee, as appropriate.

12.4 Handling of Personal Information

All persons involved in this study, including outside parties, will comply with the Act on the Protection of Personal Information and related notifications. Personal information must not be obtained by deception or other improper means, and all reasonable efforts will be made to protect the participant's personal information and privacy. Personal information learned in the course of this study must not be disclosed without legitimate reason, even after personnel leave their positions. Study personnel must not handle personal information obtained through the study beyond the scope of consent previously provided by the participant. Investigators must specify the purpose of use of personal information as clearly as possible, keep it accurate and up to date within the scope necessary to achieve that purpose, and implement measures to prevent leakage, loss, or damage and otherwise ensure proper management of personal information; the methods of such measures will be defined in written procedures.

12.5 Method of Information Processing and Management

Information obtained from participants in this study will be identified by a unique number newly assigned at registration (participant identification code), without using any information that could directly identify a specific individual. Each site investigator will prepare and securely store, in a locked location within the participating institution, a correspondence table linking the participant's name with the participant identification code.

13. Handling and Retention of Records (including data)

13.1 Provision of Samples / Information to Other Institutions for the Intended Purpose

Recipient institution: Tokyo Women's Medical University Hospital
Responsible person: Kenichi Todo
Items to be provided: information only (demographic characteristics, background factors, medical history, concomitant medications, laboratory data, imaging data, and the occurrence of outcome events or adverse events).

13.2 Storage and Disposal of Samples / Information

13.2.1 Retention of records

The site principal investigator will retain study-related records together with the following documents for 10 years from the date the study ends (the date on which the summary of the final study report is made public on jRCT), until notification of completion of the retention period is received from the coordinating investigator. The coordinating investigator will share the date of expiration of the retention period with the site principal investigators.

- Participant identification code list, protocol, implementation plan, explanatory documents for participants, consent-related documents, final study report, and other documents prepared by the site principal investigator or copies thereof in accordance with the Clinical Trials Act and related regulations

- Documents concerning review-opinion operations received from the JIHS Certified Clinical Research Review Board
- Monitoring and audit documents
- Source documents
- Contracts related to conduct of this study
- Documents describing the medical products used in this study and records prepared or obtained in relation to them
- Other documents necessary for conduct of this study

13.2.2 Retention period and place of records
The site principal investigator will appropriately retain the records specified in Section 13.2.1 in a locked storage area within the participating institution for 10 years from the date the end (or discontinuation) of the study was reported. When storage is outsourced to an external vendor, contractual arrangements will ensure that the materials can be reviewed whenever necessary and that they are maintained under appropriate conditions throughout the required retention period.

13.2.3 Methods for disposal of samples / information
When disposing of samples or information related to this study, sufficient care will be taken in handling personal information. Samples used in this study will be disposed of appropriately according to institutional procedures. Paper records will be shredded. Electronic media will be disposed of in an unreadable state, and files stored on computers will be completely deleted in a manner that prevents restoration.

14. Payments and Compensation Related to the Conduct of the Clinical Study
14.1 Participant Costs / Support for Participant Burden
This study does not involve off-label drug administration or examinations outside insurance coverage, and the frequency of testing and clinic visits is comparable to ordinary clinical care. Participants will bear costs according to the type of health insurance in which they are enrolled.

14.2 Insurance Coverage
In accordance with the Clinical Trials Act, insurance or other necessary measures will be arranged to compensate participants for health injuries related to the study. Clinical trial insurance is planned for this study; if a participant experiences health injury, compensation is expected to be provided under that insurance. Whether compensation is available and its scope will be determined individually based on the insurance contract, policy terms, and the nature and circumstances of the injury.

14.3 Compensation Other Than Insurance
If a certain level of health injury occurs as an adverse drug reaction despite appropriate use, the participant may be eligible for benefits under the Relief System for Adverse Drug Reactions.

15. Public Disclosure of Information Related to the Clinical Study
15.1 Method of Disclosure
The study will be registered and publicly disclosed in jRCT, the database maintained by the Ministry of Health, Labour and Welfare.

15.2 Arrangements with the Funding Pharmaceutical Company Regarding the Content and Timing of Publication of Study Results

15.2.1 Publication of study results

The coordinating investigator will prepare a primary endpoint report or final study report and its summary within 1 year after completion of the period for collecting data for the primary endpoint or for all endpoints. After preparing the report and summary, the coordinating investigator will obtain the opinion of the JIHS Certified Clinical Research Review Board and, without delay, submit the report to the heads of the participating institutions and register the summary in jRCT. "Without delay" means within 1 month from the date the CRB states its opinion. When submitting to the heads of participating institutions, the coordinating investigator will also notify the other site principal investigators, and those investigators will promptly report the information to the heads of their own participating institutions.

15.2.2 Publication at scientific meetings and in journals

Findings from this study will be disclosed promptly by scientific presentation and/or manuscript submission. At the time of disclosure, necessary measures will be taken to protect the human rights of participants and their related parties and the rights and interests of investigators and associated persons. The presenter at scientific meetings and the first author of manuscripts will be determined by discussion. The presenter and first author must obtain review and approval from the coordinating investigator before presentation or submission. Authorship will follow ICMJE criteria, with priority given to site principal investigators and sub-investigators from higher-enrolling sites (as a guide, sites enrolling 10 or more valid cases).

16. Study Period

Enrollment period

From the date of publication in jRCT to March 31, 2027

Planned study period

From the date of publication in jRCT to December 31, 2028 (study end date: the date on which the summary of the final study report is made public in jRCT)

17. Explanation to Participants and Obtaining Consent

Before an individual becomes a participant in this clinical study, the principal or sub-investigator will provide a sufficient explanation using the explanatory document and obtain voluntary consent for participation. The purpose and significance of the study, as well as the methods and study period, will be clearly explained.

17.1 Preparation of the Explanatory Document, Consent Form, and Withdrawal Form

For a single protocol, the coordinating investigator will prepare one common format of explanatory document, consent form, and withdrawal form and obtain approval from the certified clinical research review board. These documents will be written in plain language that can be understood by participants, legally authorized representatives, and witnesses. In this study, only persons who can read Japanese, understand the Japanese explanatory document, and provide consent on that basis will be eligible. In this multi-center study, common items other than site-specific items (such as the name of the site principal investigator and local contact information) will be standardized across participating institutions so that the contents of explanation and consent are consistent.

17.2 Items to Be Explained

The explanatory materials will include the items required by Article 46 of the Regulation (items 1-18 below) and the matters described in Sections 17.3-17.9.

1. The name of the specified clinical research, the fact that the head of the participating institution has approved its conduct, and the fact that the implementation plan has been submitted to the Minister of Health, Labour and Welfare.
2. The name of the participating institution and the name and title of the site principal investigator (and, for a multi-center study, the name and title of the coordinating investigator, the names of the other participating institutions, and the names and titles of their site principal investigators).
3. The reason the individual was selected as a participant.
4. Expected benefits and disadvantages associated with participation.
5. That refusal to participate is voluntary.
6. Matters concerning withdrawal of consent.
7. That refusal to participate or withdrawal of consent will not result in disadvantageous treatment.
8. How information about the study will be publicly disclosed.
9. That, at the request of the participant or legally authorized representative, the protocol and other materials related to conduct of the study may be obtained or reviewed, and the method for obtaining or reviewing them.
10. Protection of the participant's personal information.
11. Methods for storage and disposal of samples and other materials.
12. The status of involvement described in Article 21, paragraph 1 of the Regulation: matters concerning conflicts of interest.
13. The system for handling complaints and inquiries.
14. Matters concerning costs associated with conduct of the study.
15. The availability and details of other treatments and a comparison of their expected benefits and disadvantages.
16. Compensation and medical care for health injury associated with conduct of the study.
17. Information about the certified clinical research review board that reviews the study, including the matters reviewed by the board.
18. Any other matters necessary for conduct of the specified clinical research.

17.3 Method of Obtaining Consent from Participants

Using the explanatory document approved by the certified clinical research review board, the principal or sub-investigator will explain the study in an understandable manner directly to the participant and obtain written voluntary consent for participation. At the time of consent, the participant will be given sufficient time and opportunity to decide whether to participate and to ask questions, and all questions will be answered adequately. It will be explained that consent to participate also includes consent to direct access to the participant's medical records during monitoring, auditing, and inspections by the certified clinical research review board and regulatory authorities. The investigator providing the explanation and the participant giving consent will sign and date the consent form. After consent is obtained, the investigator will retain the original consent form and provide the participant with copies of the explanatory document and consent form. Study personnel will document that copies were provided to the participant in written records such as the original consent form or the medical record.

17.4 Selection of a Legally Authorized Representative and Obtaining Consent from That Representative

If it is difficult to obtain consent from the participant because the participant lacks capacity or for another reason, but inclusion of such a participant is necessary for the purpose of the study, consent will be obtained from a legally authorized representative and a record of the relationship between the participant and the representative will be retained.

The investigator will select a legally authorized representative from among the participant's spouse, person exercising parental authority, guardian, or another equivalent person, explain the study using the approved explanatory document, and obtain written voluntary consent from that representative. As with participant consent, the representative will be given sufficient time and opportunity to decide whether to permit participation and to ask questions, and it will be explained that consent includes consent to direct access to the participant's medical records for monitoring, auditing, and regulatory inspection. The investigator who provided the explanation and the representative who consented will sign and date the consent form in the representative signature section. After consent is obtained, the original consent form will be retained and copies of the explanatory document and consent form will be provided to the representative. Study personnel will document that copies were provided in the relevant records. If the participant later becomes capable of providing consent, an explanation of the study will be given promptly and written consent will be obtained directly from the participant.

In this context, “another equivalent person” refers to a person who, in light of the individual participant’s circumstances, can be considered capable of representing the participant’s wishes and best interests. Such persons include the participant’s parents, siblings, children, grandchildren, grandparents, cohabiting relatives, persons comparable to such close relatives, and the participant’s agent (including a voluntary guardian granted the power of representation). In addition to a guardian or other person equivalent thereto, a legally authorized representative also includes, pursuant to Article 9 of the Act, the participant’s spouse and any person exercising parental authority.

17.5 Cases in Which Minors Are Included as Study Participants

Not applicable.

17.6 Secondary Use of Samples / Information

17.6.1 Possibility of secondary use of samples / information or provision to other research institutions

Biological samples collected in this study, such as blood specimens, will be discarded in accordance with procedures at each participating institution after the examinations required for this study are completed, and will not be reused. In contrast, anonymized clinical information, laboratory data, and imaging data may be reused in future academic research related to stroke after approval by the relevant ethics committee, and anonymized information may be provided to other research institutions as necessary. However, as stated in the explanatory and consent documents, if a participant does not wish secondary use, that participant's information will not be included in secondary use.

17.6.2 Procedures for secondary use of samples / information

The explanatory and consent documents will state that information collected in this study may be reused in future academic research related to stroke and may be provided to other research institutions. The participant or legally authorized representative will indicate consent or non-consent to secondary use in writing by checking the appropriate box. Information from participants who do not consent will be excluded from future secondary use and from provision to other institutions. Whenever information is secondarily used, a new research protocol will be prepared and the study will be conducted only after review and approval by the relevant ethics committee.

17.6.3 Procedures if information is transferred to the JIHS biobank

Not applicable.

17.7 Handling of Withdrawal of Consent

If a participant or legally authorized representative withdraws consent, the investigator will consult with the participant or representative while taking care not to discourage the withdrawal, confirm the reason for withdrawal where possible, and explain any examinations or other procedures specified after withdrawal. Thereafter, the withdrawal will be documented as far as possible in writing using a withdrawal form or, alternatively, recorded in written records such as the medical chart. If permission to continue using samples or information from that participant is not obtained after withdrawal, the participant will be excluded from the analysis set.

If the study results have already been published in a manuscript, or if a medical device has been implanted in the body and cannot readily be removed, or in other situations where it is impossible to fully comply with the request for withdrawal, the investigator will explain the reason to the participant or representative and seek understanding.

Requesting a reason for withdrawal may discourage such requests. Therefore, except when necessary to ensure participant safety or in similar circumstances, the withdrawal request will be honored regardless of whether the reason is provided.

17.8 When New Information That May Affect the Participant's Intention Is Obtained

If new important information relevant to ongoing consent is obtained for a participant who is already participating in the study, the principal or sub-investigator will promptly convey that information and confirm whether the participant wishes to continue participation. If necessary, the explanatory document and consent form will be revised promptly on the basis of that information and the coordinating investigator will be notified. The coordinating investigator will share the information with the site principal investigators at the other participating institutions and obtain approval of the revised explanatory document and consent form from the certified clinical research review board.

17.9 Revision of the Explanatory Document and Consent Form (with revised version number and date)

When the explanatory document or consent form is revised, the principal or sub-investigator will in principle promptly re-explain the revised documents to participants who are still in the study period and obtain renewed written voluntary consent for continued participation. However, this

will not apply to revisions that the coordinating investigator and site principal investigators judge unlikely to affect the participant's decision regarding continued participation.

18. Matters Necessary for the Proper Conduct of the Clinical Study

18.1 Conflicts of Interest

18.1.1 Organizations providing study funding, etc.

This study will be conducted with funding provided under a clinical research contract with Kowa Company, Ltd. Kowa will perform only the roles specified in the research contract with Tokyo Women's Medical University and will not be involved in study conduct, analysis, or reporting. However, safety information such as adverse events occurring during pemafibrate administration will be shared with Kowa by the principal or sub-investigator as needed during the study. After publication of the study results, Kowa may use the results, and the processed dataset underlying the results (or a copy thereof) will be provided to Kowa. Any funds not used for the study will be returned promptly to Kowa after study completion. Applications for competitive research funding may also be considered after study initiation.

18.1.2 Management of conflicts of interest

Before conducting the study, site principal investigators, sub-investigators, and others will prepare and submit documents regarding conflicts of interest arising in the study as a whole and conflicts of interest of individual investigators in accordance with the rules of their participating or affiliated institutions, including standards for conflict-of-interest management, reports concerning related companies, investigator self-declaration forms, and conflict-of-interest management plans, and will undergo institutional review. The coordinating investigator will notify all participating investigators of the relevant forms and will receive conflict-of-interest management plans that have undergone institutional review according to each site's procedures. The coordinating investigator will submit the institutional review results to the JIHS Certified Clinical Research Review Board for review and approval and will continue to confirm, appropriately manage, and disclose conflicts of interest throughout the study period.

18.2 Clinical Research for Which Obtaining Consent from Participants Is Difficult

Not applicable.

19. Ownership of Study Results

Intellectual property rights and ownership of samples and information obtained through this study will be governed by the physician-initiated research agreement concluded with Kowa Company, Ltd.

20. Reporting to the Certified Clinical Research Review Board, the Minister of Health, Labour and Welfare, and the Heads of Participating Institutions

In addition to amendment applications and reporting of illnesses, the coordinating investigator will make all reports required under the Clinical Trials Act and related laws and regulations.

20.1 Reporting of Noncompliance

Noncompliance means failure to follow applicable regulations, the protocol, or procedures (including protocol deviations and violations), as well as falsification or fabrication of study data. If it becomes clear that this study is not compliant with regulations, the protocol, or procedures, or that study data have been falsified or fabricated, the sub-investigator who becomes aware of

the matter will report it to the site principal investigator, and the site principal investigator will report it to the head of the participating institution and the coordinating investigator. When necessary, the site principal investigator or sub-investigator may act on behalf of the coordinating investigator without being precluded from doing so.

The coordinating investigator will report the occurrence and subsequent handling of noncompliance in regular reports and, if the degree of noncompliance is judged serious, will promptly seek the opinion of the JIHS Certified Clinical Research Review Board. The coordinating investigator will also provide information regarding noncompliance to the site principal investigators within the study organization, and site principal investigators will report it to the heads of their participating institutions.

Serious noncompliance means noncompliance that affects participant rights or safety or the reliability of study progress or results. However, deviations from the protocol made to avoid an immediate hazard to a participant or for other medically unavoidable reasons are not regarded as serious noncompliance.

Regardless of the content of the study, the following are considered examples of serious noncompliance:
1. Failure to obtain informed consent.
2. Failure to obtain permission from the head of the participating institution.
3. Failure to seek the opinion of the certified clinical research review board.
4. Health injury to a participant caused by deviation from the study plan.
5. Falsification or fabrication of study data.
6. Any other case judged by the certified clinical research review board to constitute serious noncompliance.

When serious noncompliance occurs, the coordinating investigator will post in jRCT the materials submitted to the JIHS Certified Clinical Research Review Board when seeking its opinion, and the head of the participating institution will publicly disclose on the institution's website the status of the response to that serious noncompliance.

20.2 Periodic Reporting
Starting from the date the implementation plan is made public in jRCT, the coordinating investigator will submit a periodic report to the JIHS Certified Clinical Research Review Board every year, within 2 months after the end of each annual period. In addition, within 1 month after hearing the opinion of the JIHS Certified Clinical Research Review Board, the coordinating investigator will register the report in jRCT and submit a periodic report to the Minister of Health, Labour and Welfare (Regional Bureau of Health and Welfare). Site principal investigators will provide the information needed to prepare the periodic report to the coordinating investigator and will report the periodic report received from the coordinating investigator to the heads of their participating institutions.

20.3 Reporting of Study Discontinuation
If the study is discontinued, the coordinating investigator will report the discontinuation to the site principal investigators in the study organization and notify the JIHS Certified Clinical Research Review Board within 10 days of the date of discontinuation. The discontinuation will

also be registered in jRCT and reported to the Minister of Health, Labour and Welfare (Regional Bureau of Health and Welfare). Site principal investigators will report study discontinuation to the heads of their participating institutions. Even if the study is discontinued, the final study report and its summary will still be prepared appropriately, and all required reporting, including illness reporting and periodic reporting, will continue until procedures for study closure are completed.

20.4 Reporting of Study Completion

Within 1 year after completion of the period for collecting data for all endpoints, the coordinating investigator will prepare a final study report and its summary and seek the opinion of the JIHS Certified Clinical Research Review Board. After hearing the board's opinion, the coordinating investigator will promptly notify the site principal investigators, who will then submit the final study report and its summary to the heads of their participating institutions. The coordinating investigator will also register the summary of the final study report in jRCT within 1 month after the JIHS Certified Clinical Research Review Board states its opinion and will submit the required report to the Minister of Health, Labour and Welfare (Regional Bureau of Health and Welfare). The coordinating investigator will inform the site principal investigators when the final study report has been made public in jRCT, and site principal investigators will report this to the heads of their participating institutions.

21. References

1. Japan Stroke Society Stroke Guidelines Committee. Japanese Guidelines for the Management of Stroke 2021.
2. Amarenco P, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020 Jan 2;382(1):9.
3. Nordestgaard BG, et al. Triglycerides and cardiovascular disease. Lancet. 2014;384:626-635.
4. Hoshino T, et al. Prognostic Role of Hypertriglyceridemia in Patients With Stroke of Atherothrombotic Origin. Neurology. 2022 Apr 19;98(16):e1660-e1669.
5. Gutierrez J, et al. Intracranial atherosclerotic stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2022 Apr;21(4):355-368.
6. Chimowitz MI, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011 Sep 15;365(11):993-1003.
7. Gao P, et al. Effect of Stenting Plus Medical Therapy vs Medical Therapy Alone on Risk of Stroke and Death in Patients With Symptomatic Intracranial Stenosis: The CASSISS Randomized Clinical Trial. JAMA. 2022 Aug 9;328(6):534-542.
8. Sampson UK, et al. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. Curr Atheroscler Rep. 2012 Feb;14(1):1-10.
9. Yamashita S, et al. Pemafibrate, a New Selective PPARalpha Modulator: Drug Concept and Its Clinical Applications for Dyslipidemia and Metabolic Diseases. Curr Atheroscler Rep. 2020 Jan 23;22(1):5.
10. Das Pradhan A, et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. N Engl J Med. 2022 Nov 24;387(21):1923-1934.
11. Hoshino T, et al. Effect of Pemafibrate on Cerebrovascular Atherosclerosis in Patients with Stroke and Hypertriglyceridemia. J Atheroscler Thromb. 2025 Jun 1;32(6):676-687.
12. Chimowitz MI, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005 Mar 31;352(13):1305-1316.

13. Johnston SC, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283-292.
14. Japan Atherosclerosis Society. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2022.
15. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991 Aug 15;325(7):445-453.
16. Kwon SU, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke. 2005 Apr;36(4):782-786.
17. Kwon SU, et al. Efficacy and safety of combination antiplatelet therapies in patients with symptomatic intracranial atherosclerotic stenosis. Stroke. 2011 Oct;42(10):2883-2890.
18. Wong KS, et al. Variability of magnetic resonance angiography and computed tomography angiography in grading middle cerebral artery stenosis. Stroke. 1996 Jun;27(6):1084-1087.
19. Akins PT, et al. Natural history of stenosis from intracranial atherosclerosis by serial angiography. Stroke. 1998 Feb;29(2):433-438.

Appendix 1. Participating Sites and Site Principal Investigators

Name	Institution	Department	Address / Telephone
Yoshiki Yagita	Kawasaki Medical School Hospital	Department of Stroke Medicine	577 Matsushima, Kurashiki, Okayama 701-0192, Japan Tel: 086-462-1111
Makoto Nakajima	Kumamoto University Hospital	Department of Neurology	1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan Tel: 096-344-2111
Hidehiro Takegawa	Dokkyo Medical University Hospital	Stroke Center	880 Kitakobayashi, Mibu, Shimotsuga-gun, Tochigi 321-0293, Japan Tel: 0282-86-1111
Junya Aoki	Saitama Medical University International Medical Center	Department of Neurology and Cerebrovascular Medicine	1397-1 Yamane, Hidaka, Saitama 350-1298, Japan Tel: 042-984-4111
Hiroo Terashi	Tokyo Medical University Hospital	Department of Neurology	6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan Tel: 03-3342-6111
Teruyuki Hirano	Kyorin University Hospital	Department of Stroke Medicine	6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan Tel: 0422-47-5511
Yohei Tateishi	Nagasaki University Hospital	Department of Neurology	1-7-1 Sakamoto, Nagasaki 852-8501, Japan Tel: 095-819-7200
Hideki Matsuoka	Kagoshima Medical Center	Department of Neurology and Cerebrovascular Medicine	8-1 Shiroyama-cho, Kagoshima 892-0853, Japan Tel: 099-223-1151
Manabu Sakaguchi	Osaka General Medical Center	Department of Neurology	3-1-56 Bandaihigashi, Sumiyoshi-ku, Osaka 558-8558, Japan Tel: 06-6692-1201
Shuhei Okazaki	Osaka National Hospital	Department of Neurology	2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan Tel: 06-6942-1331
Shuji Hino	Japanese Red Cross Saitama Hospital	Department of Neurology	1-5 Shintoshin, Chuo-ku, Saitama 330-8553, Japan Tel: 048-852-1111
Yoshinari Nagakane	Japanese Red Cross Kyoto Daini Hospital	Department of Neurology	355-5 Haruobi-cho, Marutamachi-agaru, Kamanza-dori, Kamigyo-ku, Kyoto 602-8026, Japan Tel: 075-231-5171

Yusuke Yakushiji	Kansai Medical University Hospital	Department of Neurology	2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan Tel: 072-804-0101
Yutaka Homma	Showa General Hospital	Department of Neurology	8-1-1 Hanakoganei, Kodaira, Tokyo 187-8510, Japan Tel: 042-461-0052
Tomoyuki Ohara	University Hospital Kyoto Prefectural University of Medicine	Department of Neurology	465 Kajii-cho, Kawaramachi-Hirokoji-agaru, Kamigyo-ku, Kyoto 602-8566, Japan Tel: 075-251-5111
Ryo Itabashi	Iwate Medical University Hospital	Department of Neurology and Geriatrics	2-1-1 Idaidori, Yahaba-cho, Shiwa-gun, Iwate 028-3695, Japan Tel: 019-613-7111
Yuji Ueno	University of Yamanashi Hospital	Department of Neurology	1110 Shimokato, Chuo, Yamanashi 409-3898, Japan Tel: 055-273-1111
Shigeru Fujimoto	Jichi Medical University Hospital	Department of Neurology	3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan Tel: 0285-44-2111