

PROTOCOL

Safety and efficacy of indobufen versus aspirin for cerebral small vessel disease: A randomized, double-blind, double-dummy, multicenter (SEIAS) trial protocol

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Abstract

Indobufen, a reversible multi-target platelet aggregation inhibitor with anticoagulant properties, has been shown to reduce the risk of ischemic cardiovascular and peripheral vascular diseases. However, its efficacy and safety in patients with imaging-confirmed cerebral small vessel disease (CSVD) remain unclear. This trial protocol aims to compare the efficacy and safety of indobufen versus aspirin in patients with imaging-confirmed CSVD. We will conduct a randomized, double-blind, double-dummy, multicenter trial at 16 stroke centers in China. A total of 1,042 eligible patients will be randomly assigned in a 1:1 ratio to receive either indobufen (100 mg twice daily) or aspirin (100 mg once daily) for one year and will be followed for a total of three years. Randomization will be centrally generated by computer and stratified by participating center. The primary endpoint is the occurrence of new lacunar infarctions detected by neuroimaging within one year. Secondary endpoints include other ischemic vascular events (e.g., transient ischemic attack and myocardial infarction), cognitive impairment, and incident dementia. The primary safety outcome is hemorrhagic complications during follow-up.

Trial registry number: ChiCTR2200055893 (www.chictr.org.cn)**Keywords:** Antiplatelet agents; Cerebral small vessel disease; Lacunar stroke; Randomized controlled trial; Clinical outcomes

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1. Introduction

Cerebral small vessel disease (CSVD) accounts for approximately 25% of all ischemic strokes and is a major contributor to vascular dementia. It refers to any pathologic process that damages small perforating arteries, arterioles, venules, and brain capillaries.^{1,2} Characteristic imaging features include lacunar infarcts, white matter hyperintensities,

cerebral microbleeds, enlarged perivascular spaces, and brain atrophy.³ Given the high recurrence rate of lacunar stroke, patients with CSVD may suffer from long-term intellectual and physical disabilities, which impose a substantial disease burden.⁴ Recent studies have shown that a higher CSVD burden is associated with more severe white matter damage and worse cognitive performance.^{5,6}

Despite this, few established therapies for CSVD can effectively reduce adverse clinical outcomes, largely due to a limited understanding of its pathophysiology.⁷ Endothelial dysfunction has been proposed as a key mechanism underlying CSVD.⁸ It may lead to impaired vasoreactivity, blood–brain barrier disruption, chronic cerebral hypoperfusion, and subsequent white matter injury.^{9,10} In addition, inflammation and oxidative stress are increasingly recognized as contributors to disease progression.^{11,12} These mechanisms are believed to be involved in the development of lacunar infarcts, white matter hyperintensities, cognitive impairment, and recurrent stroke, and may represent potential therapeutic targets for CSVD.⁷

Current treatments mainly focus on controlling modifiable risk factors such as hypertension, diabetes, and smoking.¹³ Aspirin is recommended as the first-line secondary prevention strategy for cerebral infarction by current guidelines.^{14,15} However, its efficacy against lesions in small perforating arteries remains controversial. The risk of recurrent stroke among patients receiving aspirin alone is reported to be 2.7% per year.¹⁶ Furthermore, as a non-selective inhibitor of cyclooxygenase (COX-1), aspirin is associated with potential adverse events (AEs), including gastrointestinal and cerebral hemorrhage. In addition, its clinical benefit may be limited in certain populations due to drug interactions and genetic mutations leading to aspirin resistance.¹⁷ Therefore, alternative antiplatelet agents are urgently required.

Indobufen, a phenylbutyric acid derivative, exerts both antiplatelet and anticoagulant effects. It reversibly inhibits COX-1 while sparing the production of prostacyclins, which is different from aspirin.¹⁸ The incidence of gastrointestinal reactions and bleeding associated with indobufen has been reported to be lower than that with aspirin. Moreover, the inhibitory effect of indobufen is transient, and the platelet function can be recovered within 24 h after withdrawal, significantly reducing the risk of bleeding.¹⁹ A multicenter clinical study in Australia found that indobufen can significantly reduce the incidence of transient ischemic attack and prevent ischemic cardio-cerebrovascular disease more effectively and safely.^{20,21} It has also been found that indobufen plays a role in anticoagulation by reducing the plasma levels of the coagulation factors such as factors II

and X.²² Studies also found that indobufen had multiple effects, including protecting the arterial endothelium, regulating brain immune inflammation, and reducing the permeability of the blood–brain barrier.^{19,23} These might be beneficial for slowing the progression of CSVD, considering its potential pathophysiology of endothelial dysfunction, inflammation, blood–brain barrier failure, and impaired vasoreactivity.

Our unpublished small-sample study suggested that indobufen may reduce stroke recurrence and cognitive decline in aspirin-resistant lacunar infarction. Although these preliminary findings were not powered for statistical significance, they informed our rationale for the present trial comparing indobufen and aspirin in CSVD. Therefore, we select indobufen, a reversible and multi-target inhibitor of thrombosis, for the treatment of CSVD. We aim to investigate the differences in efficacy and safety between indobufen and aspirin in CSVD patients with recurrent lacunar infarctions. This indobufen vs. aspirin in CSVD trial is a multicenter, randomized, double-blind, double-dummy, large-sample, and long-term follow-up trial integrated with risk factors, clinical prognosis, and neuroimaging data. We hypothesize that indobufen is superior to aspirin in reducing the risk of new stroke, improving cognitive function, and slowing the progression of white matter hyperintensities in CSVD patients.

2. Methods

2.1. Study design

The Safety and Efficacy of Indobufen versus Aspirin for Cerebral Small Vessel Disease (SEIAS) trial is a prospective, randomized, double-blind, double-dummy multicenter clinical trial conducted at 16 stroke centers in China. This trial aims to evaluate the efficacy and safety of indobufen as compared with aspirin in patients with CSVD. A total of 1,042 patients will be randomly assigned in a 1:1 ratio to indobufen or aspirin. Patients will receive the study drug for 1 year, followed by an additional 1 to 2 years of standard care, for a total follow-up of 2 to 3 years. After the one-year treatment period, further treatment will be managed according to routine clinical practice at the discretion of the treating physicians. Information on subsequent medication use will be collected throughout follow-up. Recruitment began in 2021, and more than 600 patients have been recruited. The study flow chart is shown in [Figure 1](#).

2.2. Patient population

The inclusion criteria are:

- (i) Age between 45 and 80 years;
- (ii) Capacity to give consent;

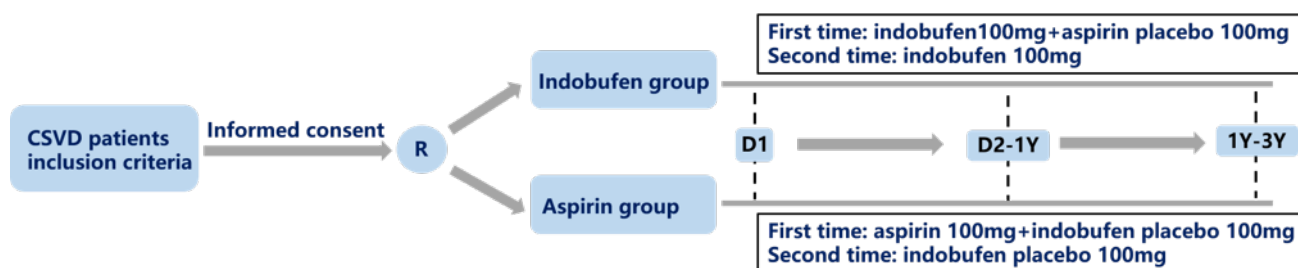


Figure 1. Flow chart of SEIAS clinical trial. Image created by the authors with Microsoft PowerPoint.
Abbreviation: CSVD: Cerebral small vessel disease.

- (iii) Patients may be symptomatic or asymptomatic. When present, CSVD-related manifestations may include dizziness, gait instability, depression, or cognitive decline; and
- (iv) Imaging-confirmed CSVD, defined by contemporaneous brain magnetic resonance imaging (MRI) demonstrating both of the following:
 - (a) A minimum of two non-acute lacunar infarction (5–15 mm in diameter, beyond the brainstem), confirmed at least three weeks post-acute infarction; and
 - (b) evidence of white matter hyperintensities of at least moderate severity, defined as a modified Fazekas scale score of 2 or 3.

Additional findings (not mandatory for inclusion) may include enlarged perivascular spaces or fewer than 10 cerebral microbleeds.

The exclusion criteria include:

- (i) Patients with more than stenosis of intracranial or extracranial arteries;
- (ii) Cognitive impairment or dementia due to neurodegenerative diseases;
- (iii) History of acute cerebral infarction, symptomatic non-traumatic intracranial hemorrhage, or cerebral amyloid angiopathy;
- (iv) History of coagulation disorders, systemic bleeding, thrombocytopenia, or neutropenia;
- (v) Gastrointestinal bleeding within six months prior to randomization;
- (vi) Major surgery performed within 30 days prior to randomization;
- (vii) Severe hepatic or renal dysfunction, defined as: glutamic-pyruvic transaminase (ALT) > 3× upper limit of normal (ULN) or aspartate aminotransferase (AST) > 2× ULN; creatinine > 2× ULN;
- (viii) History of cardiogenic embolism, such as atrial fibrillation and atrial myxoma;
- (ix) Diagnosed or suspected acute coronary syndrome;

- (x) Planned use of other antithrombotic treatment during the study period, including antiplatelet drug treatment (such as open-label aspirin, glycoprotein (GP)IIb/IIIa inhibitors, clopidogrel, ticagrelor, prasugrel, dipyridamole, ozagrel, cilostazol) and anticoagulant treatment (such as warfarin, thrombin and Xa factor inhibitors, bivaludine, Hirudin, agatroban, ordinary heparin, and low molecular heparin);
- (xi) Use of heparin or oral anticoagulants within 10 days before randomization;
- (xii) Allergy to the drug components of this study;
- (xiii) Planned revascularization (e.g., angioplasty, vascular surgery) within three months post-randomization;
- (xiv) Expected long-term (>7 days) use of non-steroidal anti-inflammatory drugs during the study;
- (xv) Severe cardiovascular or pulmonary disease deemed unsuitable for the study by the investigator;
- (xvi) History of malignancy, life expectancy < 3 months, or other conditions preventing study completion;
- (xvii) Pregnant or breastfeeding women, women of childbearing age not taking contraception;
- (xviii) Participation in other drug or device trials within 30 days prior to randomization; and
- (xix) Mental disorders that prevent comprehension of/or adherence to study procedures and follow-up.

The exit criteria are:

- (i) Patient decision. Patients can discontinue treatment at any time, provided that it does not affect further treatment.
- (ii) The researcher has decided, including but not limited to the following situations:
 - (a) Occurrence of pregnancy, death, or loss to follow-up;
 - (b) An incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk;
 - (c) Serious non-compliance with the research protocol;

- (d) Adverse events that may put patients at a higher risk of continuing treatment;
- (e) Anticoagulant treatment is required clearly; and
- (f) Researchers determined that the patient should not resume the study medication after temporarily discontinuing the medication.

2.3. Randomization

Subjects will be randomly assigned in a 1:1 fashion to receive indobufen or aspirin. The randomization sequence has been computer-generated and stratified by participating centers. Each sub-center will strictly assign random codes in ascending order and provide treatment kits corresponding to the random codes.

2.4. Blinding and unblinding

This study adopts a double-blind design, in which the investigators, participants, outcome assessors, and statisticians will remain blinded to treatment assignments throughout the trial. All active drugs and corresponding placebos will be identical in appearance, packaging, and administration to ensure blinding. Study medications will be sealed and labeled to prevent identification.

Unblinding is only permitted in emergencies, such as serious adverse events (SAEs) or when urgent treatment adjustments are needed. Investigators should contact the study monitor before unblinding whenever possible. All communications related to unblinding will be documented by the contract research organization (CRO). All unblinding events must be documented with the date, time, and reason, and the participant will be withdrawn from the study medication.

2.5. Treatments

2.5.1. Study drug information

The investigational drug is the indobufen tablet:

- Packaging presentation: 7 tablets/box, 0.2 g/tablet
- Storage condition: Store in a tightly closed container below 25 °C

The comparator is aspirin enteric-coated tablets (Bayaspirin):

- Packaging presentation: 30 tablets/box, 0.1 g/tablet
- Storage condition: Store in a tightly closed container below 25 °C

2.5.2. Method of administration

Participants will be randomly assigned to receive either indobufen or aspirin at a 1:1 ratio. The duration of medication is one year, with a follow-up period of at least

one year. Detailed method of administration is shown in Table 1. The two groups are:

- (i) Indobufen group: Oral administration, indobufen 100 mg twice a day + aspirin placebo 100 mg once a day.
- (ii) Aspirin group: Oral administration, indobufen placebo 100 mg twice a day + aspirin 100 mg once a day.

Table 1. Treatment administration in the indobufen group and the aspirin group

Drug	Duration	Remark
Indobufen	Day 1 to 360 ± 15	Morning: indobufen 100 mg + aspirin placebo
		Evening: indobufen 100 mg
Aspirin	Day 1 to 360 ± 15	Morning: aspirin 100 mg + indobufen placebo
		Evening: indobufen placebo

2.5.3. Drug management and storage

All study drugs are sponsored by Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd. (China). Study drugs will be managed uniformly by authorized researchers in accordance with clinical trial requirements and stored in a secure location. The study drugs provided in this study should be used only in accordance with the study protocol. Researchers will take inventory of study drugs distributed to patients and those returned by patients. At each visit, patients will be asked to bring all unused study drugs and empty packages to the study hospital. Researchers will verify the number of returned tablets and assess treatment compliance for the patients. For patients with poor compliance, the importance of taking study drugs as prescribed will be emphasized. Intentional or accidental destruction of study drugs must be recorded. Destruction of study drugs can only be carried out by authorized locations.

2.5.4. Packaging and labeling

Each subject's medicine box will be used for the first day through 360 ± 7 days, and the drug content will be as follows: kit 1 and kit 2 are disclosed. Kit 1 contains 15 plates of non-publicly labeled indobufen (200 mg/tablet, 7 pieces/plate); Kit 2 contains 7 plates of non-publicly labeled aspirin (15 tablets/plate):

(i) Indobufen group:

- Kit 1: A total of 15 plates of non-publicly labeled indobufen (200 mg/tablet, 7 tablets/plate)
- Kit 2: A total of 7 plates of non-publicly labeled aspirin placebo (15 tablets/plate)

(ii) Aspirin group:

- Kit 1: A total of 15 plates of non-publicly labeled indobufen placebo (7 tablets/plate)
- Kit 2: A total of 7 plates of non-publicly labeled aspirin (100 mg/tablet, 15 tablets/plate)

2.5.5. Concomitant therapy

All concomitant medications will be recorded in detail at baseline and at follow-up. Detailed information on antiplatelet use will be recorded from randomization to the end of the study. Planned concomitant treatment with any other antiplatelet agents, anticoagulants, thrombolytic therapy, batroxobin, defibrinogenase, snake venom preparations, lumbrokinase, and non-steroidal anti-inflammatory drugs (COX1 and COX2 inhibitors) is not permitted in this study. If such interventions are necessary after three months of randomization, the study drug should be discontinued five days before the intervention is implemented. Any drugs other than those listed above are permitted.

2.6. Screening period

After obtaining the informed consent form, screening will be performed to collect relevant medical histories, surgical histories, demographic data, vital signs, body weight, body mass index, National Institutes of Health Stroke Scale (NIHSS) score, pre-onset modified Rankin Scale (mRS) score, electrocardiogram, laboratory tests, and brain imaging to confirm whether the patient meets the inclusion/exclusion criteria. The randomization process will be performed after successful screening. Concomitant medications, as well as AEs, SAEs, and endpoint events, will be recorded.

2.7. Follow-up

All participants will be followed for three years after randomization. Follow-up assessments will be conducted at 90 ± 7 days, 180 ± 7 days, 1 year, 2 years, and 3 years (Table 2). The 3-month (90 ± 7 days) visit will be completed by telephone interview, whereas the subsequent visits will be conducted face-to-face at the participating study centers. The study treatment period will last for one year. After completion of the study treatment, further treatment will be managed according to routine clinical practice at the discretion of the treating physicians. Information on subsequent medication use will be collected throughout follow-up.

At each follow-up visit, information regarding new cerebrovascular events, other vascular events, current medications, treatment compliance, AEs, and SAEs will be recorded. Neurological function and disability status will be assessed using the NIHSS and mRS. Stroke subtype

classification will be updated according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria when appropriate.

Neuroimaging assessments will include brain MRI with diffusion-weighted imaging (DWI), T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI) sequences. Brain computed tomography (CT) may also be performed when clinically indicated. Neuroimaging assessments will be used to evaluate the occurrence of new lacunar infarctions and the progression of CSVD-related imaging markers, including white matter hyperintensities, enlarged perivascular spaces, cerebral microbleeds, and brain atrophy.

Cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). Psychological status will be evaluated using the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA). Gait performance will be assessed using the Tinetti Balance Scale, Tinetti Gait Scale, and Timed Up and Go (TUG) test. Urinary and bowel symptoms will be evaluated using the International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), and Cleveland Clinic Constipation Score (CCS). Health-related quality of life will be assessed using the EuroQol Five-Dimension questionnaire (EQ-5D-5L).

Laboratory assessments will include routine blood tests, coagulation parameters, liver function tests, and renal function tests. Cardiovascular evaluations will include standard 12-lead electrocardiography and 24-h ambulatory electrocardiographic monitoring according to the study schedule. Carotid ultrasonography will also be performed when required.

To minimize loss to follow-up, participants will be contacted regularly throughout the study period, and multiple contact methods, including telephone calls and outpatient visits, will be used whenever appropriate. Contact information for participants and alternative contacts will be collected at enrollment. Follow-up reminders will be provided before scheduled visits, and study coordinators at each participating center will actively track missed visits and attempt to re-establish contact with participants who cannot be reached initially.

Given the long-term follow-up and repeated neuroimaging assessments required in this study, some attrition is anticipated. In cases of incomplete follow-up or missing assessments, available clinical and imaging data will continue to be collected whenever possible. The extent and reasons for missing data will be documented

and summarized, and appropriate statistical methods will be considered to evaluate the potential impact of missing data on study outcomes.

2.8. Study endpoints

The primary efficacy outcomes will be new-onset lacunar infarctions detected by neuroimaging within one year, including both symptomatic and asymptomatic lesions.

Secondary efficacy outcomes will be:

- (i) New-onset lacunar infarctions detected by neuroimaging within three years.
- (ii) New-onset cognitive impairment or dementia within 1, 2, and 3 years, assessed by standardized cognitive assessments.
- (iii) Progression of CSVD neuroimaging markers at 1,

2, and 3 years, including increased white matter hyperintensity volume, new enlarged perivascular spaces, and new cerebral microbleeds.

- (iv) Other ischemic vascular events during the three-year study period, including transient ischemic attack, myocardial infarction, and other clinically relevant ischemic events.

Regarding safety outcomes, primary safety outcomes will be all hemorrhagic complications (including cerebral hemorrhage, gastrointestinal hemorrhage, nasal hemorrhage, urethral hemorrhage, etc). Secondary safety outcomes will be hepatic or renal dysfunction, new cerebrovascular events, AE/SAEs, and all-cause mortality.

In detail, the primary efficacy outcome is the occurrence of new-onset lacunar infarctions detected

Table 2. Study schedule

Parameter	Screening visit	Day 0	D90 ± 7 days	D180 ± 7 days	1 year ± 15 days	2 year ± 15 days	3 year ± 15 days
Informed consent signed	√						
Demographic characteristics	√						
Inclusion/Exclusion criteria	√						
Randomization	√						
Medical history	√						
Physical examination	√			√	√	√	√
ECG	√						
mRS	√		√	√	√	√	√
NIHSS	√			√	√	√	√
TOAST	√			√	√	√	√
Current medications	√		√	√	√	√	√
Brain CT/MRI	√				√	√	√
Laboratory tests	√				√	√	√
Cognitive assessments		√		√	√	√	√
Psychological scale assessments		√		√	√	√	√
Gait assessment		√		√	√	√	√
Urinary and bowel symptom assessments		√		√	√	√	√
EQ-5D-5L		√		√	√	√	√
New cerebrovascular events	√		√	√	√	√	√
AEs/SAEs	√	√	√	√	√	√	√
Treatment compliance		√	√	√	√	√	√

Abbreviations: AE: Adverse event; CT: Computed tomography; ECG: Electrocardiogram; EQ-5D-5L: EuroQol 5-Dimension 5-Level questionnaire; MRI: Magnetic resonance imaging; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SAE: Serious adverse event; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

by neuroimaging within one year after randomization, including both symptomatic and asymptomatic lesions. Brain MRI examinations will be performed according to the study schedule using standardized imaging protocols. MRI sequences will include DWI, T1WI, T2WI, FLAIR, and SWI. New lacunar infarctions will be identified by comparison with baseline imaging and defined as newly detected round or ovoid subcortical lesions measuring 3–15 mm in diameter in the territory of a perforating arteriole.

To ensure consistency across participating centers, all neuroimaging data will be stored in DICOM format and transferred to the coordinating center for centralized review. Image assessment will be performed by trained neuroradiologists who are blinded to treatment allocation and clinical outcomes. In cases of uncertainty or disagreement, a consensus review will be conducted. MRI scans with incomplete sequences or inadequate image quality will be documented, and their potential impact on endpoint assessment will be considered during data analysis.

Secondary efficacy outcomes include the occurrence of new lacunar infarctions during the entire 3-year study period, cognitive impairment or dementia at 1, 2, and 3 years, progression of CSVD-related neuroimaging markers, and other ischemic vascular events. Progression of CSVD imaging markers will be assessed on serial MRI examinations and will include increases in white matter hyperintensity burden, newly developed enlarged perivascular spaces, newly developed cerebral microbleeds, and other imaging manifestations of disease progression. Other ischemic vascular events, including transient ischemic attack and myocardial infarction, will be recorded throughout follow-up.

Primary safety outcomes include all hemorrhagic complications, including intracranial, gastrointestinal, nasal, and urinary tract hemorrhage. Secondary safety outcomes include hepatic dysfunction, renal dysfunction, new cerebrovascular events, AEs, SAEs, and all-cause mortality. All efficacy and safety outcomes will be prospectively collected and adjudicated according to predefined study procedures.

2.9. Safety considerations

If AEs occur, the study investigators need to treat the patients and report them to the principal investigator (PI) immediately. The AE details need to be fully recorded in documents, including grades, dates, treatment process, and outcomes. SAEs refer to the adverse medical events such as death, life-threatening conditions, permanent or severe disability or loss of function, and hospitalization

or prolonged hospital stay. All SAEs will be recorded and reported to the sponsor, clinical trial institution office, and ethics committee within 24 h.

Adverse events and adverse drug reactions will be reviewed by two independent specialists of the safety monitoring board (DSMB), who will be unblinded to the medication. DSMB determines whether to terminate the study prematurely by reviewing AEs and endpoint events to ensure the rights and interests of the subjects. Subject information is strictly protected throughout the research process and data analysis process. The results of the trial after the database is locked will be announced as soon as possible. Data monitoring is conducted by the Ethics Committee of Drum Tower Hospital.

2.10. Sample size

The sample size was calculated based on the primary efficacy outcome, namely the occurrence of new lacunar infarctions detected by neuroimaging within one year after randomization. A large nationwide observational study reported a one-year recurrent ischemic stroke rate of 11.3% among patients with ischemic stroke.²⁴ In the absence of robust contemporary data, specifically in patients with lacunar infarction, the one-year recurrent ischemic stroke rate reported in a large nationwide observational study was used as the reference event rate for sample size calculation. As no randomized trial specifically evaluating indobufen for the prevention of new imaging-detected lacunar infarctions was available at the time of study design, an absolute risk reduction of 3% (from 11.3% to 8.3%) was assumed based on clinical considerations and the known pharmacological effects of indobufen. This effect size was considered clinically meaningful and achievable within the study population.

Using a one-sided alpha level of 0.025 and a statistical power of 80%, a total of 938 participants will be required to detect this difference. To account for potential loss to follow-up, treatment discontinuation, or incomplete imaging assessments during the three-year study period, the sample size was increased by 10%, resulting in a final target enrollment of 1,042 participants, with 521 participants allocated to each treatment group. The rationale for the assumed dropout rate was based on prior experience with multicenter cerebrovascular studies and the anticipated feasibility of follow-up at participating centers. To minimize loss to follow-up, participants will be actively contacted and reminded of scheduled visits throughout the study period. Missing data and reasons for withdrawal will be recorded, and appropriate statistical methods will be used to address the potential impact of missing data on study outcomes.

All participants will provide written informed consent to participate in this study. Written informed consent will be obtained from all participants or their legal representatives by trained investigators before inclusion in the study. Participants will be informed about the study's purpose, procedures, potential risks, and benefits.

2.11. Statistical analyses

This study is designed as a superiority trial. Efficacy analyses will be conducted in both the intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population will include all randomized participants and will serve as the primary analysis population. The PP population will include participants who complete the study without major protocol deviations and with adequate treatment adherence. Safety analyses will be performed in all participants who receive at least one dose of the study medication.

Continuous variables will be summarized using descriptive statistics, including mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum values, as appropriate. Categorical variables will be summarized using frequencies and percentages. Statistical methods for efficacy and safety endpoints are described below. Treatment effects will be presented with corresponding 95% confidence intervals (CIs). Unless otherwise specified, all statistical tests will be two-sided, and a p -value < 0.05 will be considered statistically significant.

2.11.1. Primary efficacy analyses

The primary efficacy analysis will be performed in the ITT population, with supportive analyses conducted in the PP population. The primary endpoint is the occurrence of new-onset lacunar infarction detected by neuroimaging within one year. The incidence of the primary endpoint will be compared between treatment groups using the Chi-square test or Fisher's exact test, as appropriate. Treatment effects will be expressed as odds ratios (ORs) and relative risks (RRs), along with corresponding 95% CIs. As this is a superiority trial, superiority of indobufen over aspirin will be concluded if the upper limit of the two-sided 95% CI for the risk difference (RD) is less than 0, corresponding to a statistically significant reduction in the incidence of new-onset lacunar infarction (two-sided $p < 0.05$) in the ITT population.

Results from the PP population will be considered supportive evidence for the robustness of the findings. As a supportive analysis, a multivariable regression model will be performed, adjusting for prespecified baseline covariates, including age, sex, hypertension, diabetes

mellitus, and baseline CSVD imaging burden. Time-to-event analyses will be conducted using Kaplan–Meier methods and compared using the log-rank test. Hazard ratios (HRs) and 95% CIs will be estimated using Cox proportional hazards models.

2.11.2. Secondary efficacy analyses

(a) New-onset lacunar infarctions within three years

The incidence of new-onset lacunar infarctions detected by neuroimaging within three years will be compared between treatment groups using the Chi-square test or Fisher's exact test, as appropriate. Treatment effects will be reported as RD, RR, OR, and corresponding 95% CIs. Adjusted RRs and adjusted ORs will be estimated using modified Poisson regression with robust variance and multivariable logistic regression, respectively, adjusting for prespecified baseline covariates. Time-to-event analyses will be performed using Kaplan–Meier methods and Cox proportional hazards models, with HRs and corresponding 95% CIs reported.

(b) New-onset cognitive impairment or dementia

The incidence of new-onset cognitive impairment or dementia within 1, 2, and 3 years will be compared between treatment groups using the Chi-square test or Fisher's exact test. Treatment effects will be reported as RD, RR, OR, and corresponding 95% CIs. Adjusted RRs and adjusted ORs will be estimated using modified Poisson regression with robust variance and multivariable logistic regression, respectively. Longitudinal changes in cognitive assessment scores will be analyzed using linear mixed-effects models, including treatment group, visit, and treatment-by-visit interaction as fixed effects and participant as a random effect. Treatment effects for continuous cognitive outcomes will be expressed as mean differences (MDs) between groups with corresponding 95% CIs.

(c) Progression of cerebral small vessel disease neuroimaging markers

Progression of CSVD neuroimaging markers at 1, 2, and 3 years, including increased white matter hyperintensity volume, newly enlarged perivascular spaces, and newly formed cerebral microbleeds, will be evaluated. For continuous imaging outcomes, treatment effects will be estimated as MDs with corresponding 95% CIs. Adjusted analyses will be performed using linear mixed-effects models adjusted for baseline values and other prespecified covariates. For binary imaging outcomes, treatment effects will be reported as RD, RR, OR, and corresponding 95% CIs. Adjusted RRs and adjusted ORs will be estimated using modified Poisson regression with robust variance and multivariable logistic regression, respectively.

(d) Other ischemic vascular events

The incidence of other ischemic vascular events during the

three-year follow-up period, including transient ischemic attack, myocardial infarction, and other clinically relevant ischemic events, will be compared between treatment groups using the Chi-square test or Fisher's exact test. Treatment effects will be reported as RD, RR, OR, and corresponding 95% CIs. Adjusted RRs and adjusted ORs will be estimated using modified Poisson regression with robust variance and multivariable logistic regression, respectively. Time-to-event outcomes will additionally be analyzed using Kaplan–Meier methods and Cox proportional hazards models, with HRs and corresponding 95% CIs reported.

2.11.3. Safety analyses

Safety outcomes will include hemorrhagic events, liver dysfunction, renal dysfunction, SAEs, and all-cause mortality. For binary safety outcomes, treatment effects will be reported as RD, RR, OR, and corresponding 95% CIs. Adjusted RRs and adjusted ORs will be estimated using modified Poisson regression with robust variance and multivariable logistic regression, respectively. Time-to-event safety outcomes will be analyzed using Kaplan–Meier methods and Cox proportional hazards models, with HRs and corresponding 95% CIs reported.

2.11.4. Missing data

For the primary endpoint, participants with missing outcome data will be included in the ITT analysis. If the proportion of missing primary endpoint data is less than 5%, complete-case analysis will be performed. If the proportion of missing data is 5% or greater, multiple imputation using chained equations (MICE) will be applied under the missing-at-random assumption. Sensitivity analyses, including complete-case analysis and worst-case/best-case imputation scenarios, will be conducted to assess the robustness of the results.

For secondary endpoints, complete-case analyses will be performed when the proportion of missing data is less than 5%. If the proportion of missing data is 5% or greater, multiple imputation will be used for cross-sectional outcomes. For longitudinal repeated-measures outcomes, mixed-effects models will be used, as these models can appropriately handle missing observations under the missing-at-random assumption.

3. Discussion and summary

Prevention of recurrent lacunar infarction remains a major challenge in patients with CSVD. Although antiplatelet therapy is widely recommended for secondary prevention, the optimal antiplatelet strategy for patients with CSVD has not been established.^{25,26} Aspirin remains the most

commonly used agent²⁷; however, its long-term use is frequently limited by hemorrhagic complications and gastrointestinal adverse effects.^{28–30}

Indobufen is a selective and reversible COX-1 inhibitor that effectively inhibits platelet activation, aggregation, and adhesion, which may be associated with a lower risk of gastrointestinal adverse effects than aspirin.^{31,32} In addition to its antiplatelet activity, indobufen has demonstrated anticoagulant properties comparable to those of conventional anticoagulants in experimental and clinical studies.^{22,33} Previous studies have suggested that indobufen provides efficacy comparable to aspirin in patients with cardiovascular and peripheral vascular diseases, while being associated with fewer AEs.³⁴ More recently, the INSURE trial failed to demonstrate non-inferiority of indobufen compared with aspirin in patients with acute moderate-to-severe ischemic stroke¹⁹, highlighting the need for further evaluation of its role in specific stroke populations.

Cerebral small vessel disease differs substantially from large-artery atherosclerotic stroke and cardioembolic stroke in terms of pathophysiology, clinical manifestations, and long-term outcomes.³⁵ Recurrent lacunar infarctions contribute not only to recurrent stroke events but also to the progression of cognitive impairment and functional decline.^{36,37} Therefore, an antiplatelet agent that can effectively prevent recurrent lacunar infarction while maintaining a favorable safety profile may offer important clinical benefits in this population.^{38,39} To date, no randomized controlled trial has specifically evaluated the efficacy and safety of indobufen in patients with CSVD.

This trial is therefore designed to compare indobufen with aspirin in patients with CSVD and to determine whether indobufen can reduce recurrent lacunar infarction, slow cognitive decline, and improve long-term clinical outcomes without increasing bleeding risk. The findings of this study will provide important evidence regarding the optimal antiplatelet strategy for secondary prevention in CSVD and may help guide future clinical practice. Given the substantial disease burden associated with CSVD, including stroke recurrence, cognitive impairment, disability, and healthcare utilization^{37,40}, establishing an effective and safe preventive strategy may have significant clinical and socioeconomic implications.

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Conflict of interest

Yun Xu serves as one of the Editors-in-Chief of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

The clinical trial design is based on the Declaration of Helsinki and the Chinese Clinical Practice Guidelines. The protocol was approved by the Ethics Committee of Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School (Ethical Approval Code: 2021-446-01). If necessary, the agreement will be amended with the permission of the Ethics Committee. The study has been registered in the National Clinical Research Information Service Center of China (ChiCTR2200055893). Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research protocol. Given the nature of this randomized, double-blind clinical trial, it is not considered appropriate or feasible to involve patients or the public in these stages of the study.

Consent for publication

Not applicable.

Availability of data

All supporting data contributing to this study may be

provided by the corresponding author upon reasonable request.

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