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Evaluation of safety and efficacy of intracranial self-expanding drug-eluting stents for symptomatic intracranial atherosclerotic stenosis: a prospective, multicentre, randomised controlled, superiority clinical trial protocol

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ABSTRACT

Background In-stent restenosis (ISR) is a crucial factor that affects the long-term efficacy of intracranial bare metal stent (BMS) implantation for intracranial atherosclerotic stenosis (ICAS). Patients with intracranial ISR are at a high risk of recurrent ischaemic events. The NOVA intracranial drug-eluting stent (DES) trial demonstrates that a DES can reduce ISR and stroke recurrence after intracranial bare stent implantation. However, the application of balloon-expanded DES necessitates specific vascular conditions. The objective of this study is to assess the safety and efficacy of self-expanding DES for treating symptomatic ICAS (sICAS).

Methods This is a prospective, multicentre, randomised, controlled, superiority clinical trial that is conducted in 16 clinical trial centres in China. This study aims to recruit 208 patients with sICAS. Eligible subjects are randomly assigned to two groups at a ratio of 1:1. The experimental group is treated with DES (Xinwei intracranial DES system). The control group is treated with BMS (Wingspan intracranial stent system). All subjects are followed up within 7 days after surgery or before discharge; 30 days after surgery; and 6, 12 and 24 months after surgery. The primary outcome of the trial is the incidence of ISR at 6 months after surgery to verify the safety and efficacy of intracranial DESs. After 6 months of follow-up, the clinical summary report is issued for product registration application, and the follow-up of 12 months and 24 months after operation is conducted to evaluate the medium and long-term efficacy.

Ethics and dissemination The study involving human participants is reviewed and approved by the Ethics Committee of Drugs (devices) Clinical Experiment in Henan Provincial People's Hospital (reference number: AF/SC-08/05.0) and other research centres participating in the clinical trial (supplemental file 2). The results yield from this study will be presented at international conferences and sent to a peer-reviewed journal to be considered for publication.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a multicentre, randomised controlled design to evaluate the efficacy of an intracranial self-expanding drug-eluting stent.
⇒ The study includes comprehensive and rigorous follow-up assessments over a 24-month period.
⇒ Experienced neurointerventionalists at 16 centres will ensure consistent procedural techniques.
⇒ The experiment is conducted in China, and the included people are all Asians, which may limit the general applicability of the study results.
⇒ The treatment randomisation is not blinded to the operators, treating physicians or patients.

Trial registration number Registered on 2 November 2023 with Chinese clinical trial registry. Registration number is ChiCTR2300077271.

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is a significant cause of ischaemic stroke worldwide. ICAS accounts for 8%–10% of strokes in North America.[1–4] In China, ICAS is present in 46.6% of stroke/transient ischaemic attack (TIA) patients.[5] ICAS increases the risk of stroke occurrence and recurrence and is also a significant risk factor for poor prognosis of stroke. Several studies, including the warfarin and aspirin for symptomatic intracranial disease study and several cohort studies, have demonstrated that the risk of stroke recurrence in patients with ICAS remains high despite aggressive medical therapy and risk factor intervention.[6–8]

Endovascular treatment is considered an important method for treating ICAS. The

China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) study demonstrates that the combination of stents and medical therapy is as effective as medical therapy alone in reducing the risk of stroke or death among patients with symptomatic ICAS (sICAS).[9] One of the key concerns associated with stenting is the potential for in-stent restenosis (ISR) to occur. This is a critical factor that can significantly impact the long-term success of intracranial bare metal stent (BMS) placement for the treatment of ICAS. Patients with intracranial ISR are at high risk of recurrent ischaemic event.[10] The 1-year rate of ISR in patients with intracranial self-expandable and balloon-expandable BMSs ranges from 15% to 33%.[11–15] The use of drug-eluting stents (DESs) can reduce ISR by inhibiting the proliferation and migration of endothelial and smooth muscle cells after stent implantation.[16] The effectiveness and safety of a DES in treating coronary artery stenosis have been confirmed in the cardiovascular field.[17 18] Research and clinical applications have also begun in the field of cerebrovascular. Some single-centre retrospective studies have shown that a DES is safe and feasible in treating ICAS.[19–22] A recent randomised controlled trial (RCT) compared balloon-expanded BMSs with balloon-expanded DESs (NOVA) for the treatment of ICAS. The study found that DESs could reduce ISR and stroke recurrence after implantation of an intracranial bare stent system.[23]

There is currently no self-expanding DES specifically designed for the treatment of intracranial atherosclerotic stenosis that has been approved for real-world use. This study aims to introduce a new treatment option by conducting a RCT comparing intracranial self-expanding DESs with self-expanding BMSs for ICAS. The study's objective is to assess the safety and effectiveness of self-expanding intracranial DESs in treating ICAS.

METHODS

Objective

The objective of this study is to assess the safety and efficacy of a self-expanding DES (Xinwei intracranial DES system) for treating sICAS.

Study device

Xinwei DES is a type of self-expanding, drug-coated stent used in the treatment of ICAS. By expanding narrow blood vessels, it provides support, improves blood flow and releases drugs slowly to inhibit vascular smooth muscle cell proliferation and migration, thus preventing ISR. Xinwei DES consists of three components: the stent, the delivery guide wire and the introduction sheath. The stent is premounted on the delivery guide wire within the introduction sheath, as illustrated in figure 1.

The stent is constructed from a medical nickel-titanium alloy tube and undergoes processes such as laser engraving, heat setting, pickling and polishing. It features a closed mesh design with development marks at both ends and sometimes in the middle for certain sizes. The stent's bottom coating is made of poly-n-butyl methacrylate (PBMA), known for its excellent biocompatibility. The bottom coating enhances epithelial cell coverage on the stent and aids in wound healing. The surface coating includes polylactic acid-co-glycolic acid (PLGA), rapamycin, boron reagent and polyphosphorylcholine. PLGA is biocompatible and degradable, rapamycin inhibits smooth muscle cell proliferation and migration, boron reagent is a biocompatible dye, and polyphosphorylcholine helps prevent thrombosis.

Design and patient population

This is a prospective, multicentre, randomised, controlled, superiority clinical trial conducted in 16 medical centres in China. The planned start date of this study is November 2023, and the planned end date is December 2026. The trial aims to recruit 208 patients with sICAS. The experimental group is treated with DES (Xinwei intracranial DES system). The control group is treated with BMS (Wingspan intracranial stent system). The patients are followed up for 2 years after registration, including neurovascular imaging examination (digital subtraction angiography (DSA), MR angiography (MRA), CT angiography (CTA)) within 1 year. Patients with sICAS (defined as recent TIA or ischaemic stroke due to 70%–99% atherosclerotic stenosis of a major intracranial artery) who undergo DSA at each centre and meet the trial's inclusion/exclusion criteria are considered for inclusion in the trial. Inclusion and exclusion criteria are listed in box 1.

Randomisation

This study is a randomised controlled clinical trial that uses a central randomisation method through Internet-based Central Random System. Researchers input basic

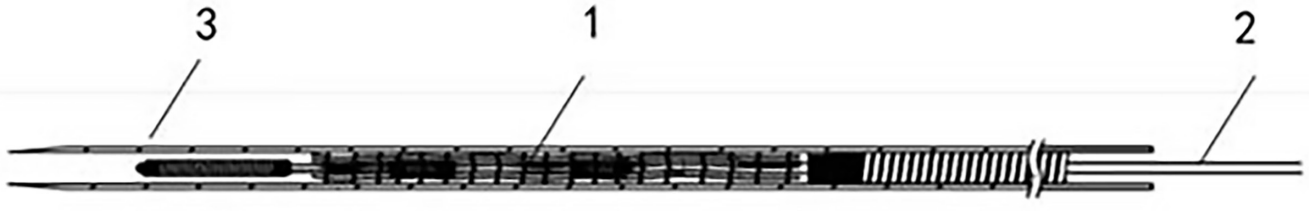

Figure 1 Diagram of intracranial drug-eluting stent (DES). (1) DES, (2) delivery guide, (3) introducer sheath. The intracranial DES can be compatible with 0.021-inch microcatheters, and some specifications can also be compatible with 0.017-inch microcatheters.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

⇒ 18–80 years old.
⇒ Patients with symptomatic intracranial atherosclerotic stenosis in the target vessel region who have failed medical treatment or have hypoperfusion with a target lesion stenosis degree of 70% ≤stenosis ≤ 99%.
⇒ The lesion requiring treatment is a single target lesion located in the intracranial segment of the internal carotid artery, the middle cerebral artery, the intracranial segment of the vertebral artery or the basilar artery.
⇒ The reference vessel diameter of the target lesion ranges from 1.5 mm to 5.0 mm, with the lesion length being ≤34 mm.
⇒ Modified Rankin Scale score ≤2.
⇒ Patients deemed suitable for endovascular stent treatment by the investigators.
⇒ The patient or their guardian voluntarily agrees to participate and signs a written informed consent, committing to the protocol-specified examinations and follow-ups.

Exclusion criteria

⇒ Patients whose target lesions have previously undergone endovascular intervention (excluding simple balloon angioplasty) or surgical treatment.
⇒ Patients with symptomatic carotid stenosis ≥50% outside the target lesion or with ≥70% stenosis in other intracranial or extracranial vessels requiring treatment.
⇒ Stroke caused by isolated perforating artery occlusion lesions.
⇒ Patients who experienced acute ischaemic stroke or severe myocardial infarction within 14 days before the procedure.
⇒ Patients who experienced intracranial haemorrhage within 3 months before the procedure.
⇒ Patients with lesions exhibiting severe calcification, severe tortuosity or extreme curvature, deemed unsuitable for device use by the investigator.
⇒ Patients with severe intracranial arterial stenosis or tortuosity or anatomical abnormalities that make it difficult for the device to reach the lesion site, as assessed by the investigator.
⇒ Patients with intracranial tumours, arteriovenous malformations, haematomas or tandem aneurysms proximal or distal to the target lesion.
⇒ Patients with known uncontrollable hypertension (persistent systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg).
⇒ Patients known to have contraindications to antiplatelet and/or anticoagulant therapy.
⇒ Patients known to have significant coagulation abnormalities or bleeding tendencies, as judged by the investigator to be unsuitable for surgery.
⇒ Patients known to have severe liver or kidney dysfunction (aspartate aminotransferase or alanine aminotransferase levels exceeding three times the upper limit of normal; creatinine >1.5 times the upper limit of normal).
⇒ Patients with a history of known allergy to materials such as rapamycin, polylactic acid-co-glycolic acid, polymethylmethacrylate, boron agents and nickel-titanium.
⇒ Patients with a history of severe allergy to anaesthetic agents or contrast agents (excluding rashes).
⇒ Patients with an expected lifespan of less than 2 years.
⇒ Pregnant or lactating women.

Continued

Box 1 Continued

⇒ Patients currently participating in other clinical studies involving drugs or devices and who have not completed the primary endpoint follow-up.
⇒ Subjects deemed unsuitable for participation in the clinical trial as assessed by the investigator.

information of eligible patients on a webpage, and the computer system automatically generates random numbers and groups. Subjects meeting inclusion criteria are randomly divided into groups in a 1:1 ratio. The experimental group receives treatment with DES (Xinwei intracranial DES system), while the control group receives treatment with BMS (Wingspan intracranial stent system) (figure 2).

Intervention technique

The patient is prescribed to take 100 mg of aspirin and 75 mg of clopidogrel orally daily for a minimum of 5 days prior to surgery. This regimen should continue until thromboelastography indicates that the patient has achieved the desired response to anti-platelet aggregation drugs, with an inhibition rate of aspirin greater than 70% and an inhibition rate of clopidogrel greater than 30%. Cerebrovascular disease risk factors will be controlled according to the 2014 American Heart Association/American Stroke Association guidelines.[24] The main risk factor control includes hypertension (systolic blood pressure <140 mm Hg (<130 mm Hg in patients with diabetes) and diastolic blood pressure <90 mm Hg) and statin therapy for dyslipidaemia (low-density lipoprotein cholesterol level <70 mg/dL). Other secondary risk factors such as glucose disorders, obesity, smoking, alcohol consumption, nutrition and physical inactivity will be managed as well.

The patient is positioned supine. After general anaesthesia, the right femoral artery is punctured, and a 6F arterial sheath is inserted. Heparin sodium is then administered intravenously for systemic heparinisation. The guiding catheter is placed distal to the origin of the internal carotid artery proximal to the lesion or proximal to the origin of the subclavian artery and proximal to the vertebral artery, and then the intermediate catheter is advanced near the proximal end of the lesion. Under the guidance of the path map, a 200-cm microguidewire with a microcatheter is used to cross the lesion to the distal blood vessel or branch, withdraw the microguidewire, insert a 300-cm microguidewire with a J-shaped tip and withdraw the microcatheter. A balloon catheter of appropriate size is sent to the stenotic lesion along the guide wire. The diameter of the balloon needs to be 80% of the diameter of the stenosis. The balloon is slowly inflated to the standard pressure. After the expansion is satisfactory, the coaxial exchange is used to remove the balloon, and a microcatheter is inserted along

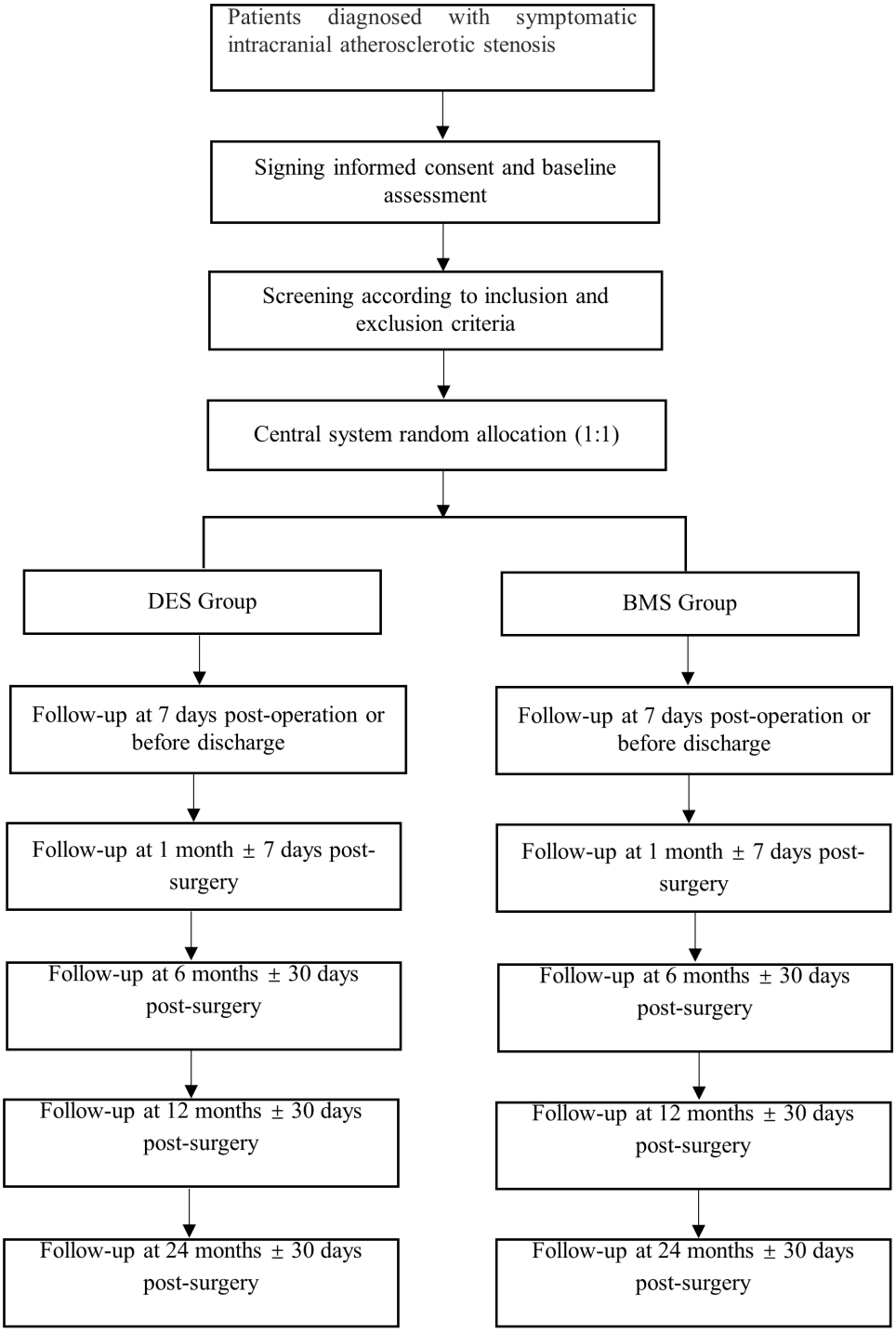

Figure 2 Flow-diagram illustrating study flow. BMS, bare metal stent; DES, drug-eluting stent.

the exchange guidewire. The Xinwei DES is delivered to the diseased area through the catheter. If it is a Wingspan stent, it does not require the cooperation of a microcatheter and can be delivered directly. The length of the stent should be able to completely cover the lesion, extending 3 to 5 mm beyond both ends of the lesion. After the position is adjusted satisfactorily, the stent is released to the lesion. After 5 min, angiography is performed to confirm the residual stenosis, and the antegrade blood flow after dilation is evaluated according to the Thrombolysis in Cerebral Infarction grading system. Successful recanalisation is defined as residual stenosis <50% and TICI grade ≥2 b. Patients with residual stenosis ≥50% will undergo in-stent balloon dilatation. After surgery, the patient continues to receive oral aspirin 100 mg and clopidogrel 75 mg daily for 6 months and then receives aspirin monotherapy for life.

Follow-up and assessment

All subjects are followed up by neurologists from each centre during preoperative screening, the operation, within 7 days after the operation or before discharge, at 30 days, 6 months, 12 months and 24 months postoperation. Follow-up is conducted through telephone or face-to-face interviews. Vital signs, medication and adverse events (AEs) are documented at each follow-up visit. Clinical events are reported by the follow-up physician and reviewed by an independent clinical events adjudication committee. At the 1-year follow-up, all patients undergo neurovascular imaging, such as DSA, CTA or MRA. The complete study evaluation schedule is presented in table 1.

Patient and public involvement

There is no patient and public involvement in this protocol.

RESULTS

Primary efficacy endpoints

The primary outcome measure in this study is the incidence of ISR at 6 months postsurgery. ISR is defined as greater than 50% stenosis of the luminal diameter within or immediately adjacent to (within 5 mm) the implanted stent with an increase of over 20% compared with the immediate postoperative residual stenosis rate.

Secondary efficacy endpoints

The study evaluates seven secondary outcomes: (1) success rate of device operation, which demonstrates successful stent implantation and coverage of the target lesion site, along with the successful withdrawal of the delivery system; (2) operation success rate, including successful stent implantation, absence of major AEs during the procedure (such as death or stroke) and immediate postoperative residual stenosis <50%; (3) ISR rate at 12 months postoperation; (4) incidence of symptomatic stent restenosis at 6 months and 12 months postoperation; (5) Modified Rankin Scale (mRS) score at 30 days, 6 months and 12 months postsurgery; (6) National Institutes of Health Stroke Scale (NIHSS) score preoperatively and 6 months posthospital discharge; and (7) target lesion revascularisation rates at 30 days, 6 months and 12 months postoperation, defined as the need for any surgical or percutaneous intervention to restore blood supply to the target vessel.

Safety outcomes

This study examines four safety indicators related to surgical outcomes: (1) stroke incidence at 30 days, 6 months and 12 months postsurgery; (2) all-cause death rates at 30 days, 6 months, 12 months and 24 months postsurgery; (3) incidence rates of device-related AEs/serious AEs at 30 days, 6 months, 12 months and 24 months postsurgery; and (4) incidence rates of device defects.

Sample size

The sample size of this trial is calculated based on the primary endpoint of the 6-month stent restenosis rate. According to the literature results and clinical experience,[25–28] the 6-month stent restenosis rate of the control group is 22%, and the 6-month stent restenosis rate of the trial group is assumed to be 7%. When the significance level of the statistical test is one-sided 2.5%, and the power is 80%, the maximum possible dropout rate of 20% is considered in the study. According to the statistical principle, 104 patients are needed to be enrolled in each group, and the total number of patients in the two groups is 208.

Statistical analysis

For descriptive analysis, enumeration data are expressed by frequency and composition ratio, while measurement data are represented by the mean, SD, maximum, minimum, median, and 25th and 75th quantiles.

For baseline demographics, the χ^2 test or Fisher's exact probability test is used to compare qualitative data between groups. The grouped t-test is employed to compare normally distributed quantitative data between groups, while the Wilcoxon rank sum test is used for comparing non-normally distributed quantitative data between groups.

The primary outcome (ISR 6 months after surgery) is analysed using the Cochran-Mantel-Haenszel χ^2 analysis to correct for the influence of the centre effect. The study estimates the difference in ISR rates between the experimental group and the control group 6 months after surgery on both sides, with a 95% CI. Statistical analysis is conducted at a one-sided significance level of 0.025, corresponding to a one-sided 95% CI. Other efficacy indicators between groups are compared in a similar manner as in the baseline analysis.

For evaluation of safety outcomes, the number and proportion of cases that are normal before treatment and abnormal after treatment are described. The number and incidence of AEs are described, and the proportion is tested by the likelihood ratio χ^2 test and Fisher's exact test. Moreover, the specific manifestations and extent of all AEs in each group and their relationship with the study devices are described in detail.

For the primary endpoint indicators, statistical analysis is performed at a unilateral significance level of 0.025 (corresponding to the unilateral confidence limit of 95% CI), and the statistical analysis of the other indicators is performed at a significance level of 0.05. SAS 9.4 statistical software is used for statistical analysis.

Assessment of adverse events

The definition of AE is the occurrence of all unexpected medical conditions during or after the use of medical devices. It includes symptoms, signs or abnormal laboratory parameters that may be unrelated to the treatment. The definition of severe AE is an AE that meets at least one of the following criteria: leads to death; requires

Table 1 Assessment schedule

Timeline items	Enrolment and treatment		Follow-up				
Window period	Preoperative screening: 15–0 day	During operation 0 day	Within 7 days postsurgery or before discharge	1 month ±7 days postsurgery	6 months ±30 days postsurgery	12 months ±30 days postsurgery	24 months ±30 days postsurgery
Informed consent††	●						
Medical history/demographic data	●						
Vital signs	●						
Blood routine test*	●		●				
Blood biochemistry†	●		●				
Routine coagulation test ‡	●						
Pregnancy test §	●						
Imaging examination ¶	DSA/CTA/MRA				DSA/CTA	CTA	
mRS score	●		●	●	●	●	
Inclusion/exclusion criteria	●	●					
Surgical treatment with instruments		●					
Device defects		●					
Combined medication records**	●	●	●	●	●	●	●
Adverse events		●	●	●	●	●	●

*Blood routine includes: white blood cell count, red blood cell count, platelet count and haemoglobin.
†Blood biochemistry includes: total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, creatinine and glucose.
‡Routine coagulation test: thrombin time, prothrombin time, activated partial thromboplastin time, international normalised ratio.
§Pregnancy tests are performed only when necessary.
¶If a subject cannot undergo DSA examination at 6 months postoperatively due to specific reasons, CTA examination may be accepted for efficacy evaluation at 6 months postoperatively; if a subject fails to return to the hospital for follow-up at 6 months or 12 months postoperatively due to specific reasons, imaging follow-up at another hospital may be accepted.
**Combined medication records only include anti-platelet agents, anti-coagulants and statins.
††The laboratory test results and scoring results within 14 days prior to signing the informed consent form are considered valid. Similarly, CTA, MRA or DSA results within 45 days prior to signing the informed consent form are also considered valid.
CTA, CT angiography; DSA, digital subtraction angiography; MRA, MR angiography; mRS, Modified Rankin Scale.

hospitalisation or extends the existing hospitalisation time; is life-threatening; and leads to serious disability or requires medical intervention to prevent one of the aforementioned outcomes. If a potential endpoint occurs, the committee board meeting will be convened to evaluate whether such an event can be categorised as the primary endpoint.

Data safety and monitoring board

The data safety and monitoring board (DSMB) members are independent of the researchers and the steering committee. DSMB is responsible for assuring that study participants are not exposed to unnecessary risks and that the study is being conducted according to high scientific and ethical standards. The DSMB is responsible for advising early termination of the study in the event of unexpected safety concerns or if treatment differences are apparent at the prespecified interim analyses.

Study organisation

An independent clinical events adjudication committee conducts blinded review and evaluation of the endpoint events occurring during the trial. Composed of clinical experts independent of both the researchers and the sponsor, this committee does not directly participate in the implementation of the clinical trial. These clinical experts are authorities in their respective clinical research fields, ensuring objectivity and independence in their adjudication.

Ethical considerations

The study involving human participants is reviewed and approved by the Ethics Committee of Drugs (devices) Clinical Experiment in Henan Provincial People's Hospital (reference number: AF/SC-08/05.0) and other research centres participating in the clinical trial (online supplemental file 2). This study is conducted in accordance with the Declaration of Helsinki and relevant national regulations. The same version of the clinical trial protocol is submitted to each centre and implemented after approval by the ethics committee. Any safety issues related to the clinical trials must be promptly reported to the ethics committee. Subjects willing to participate in the trial are required to sign an informed consent form (online supplemental file 1). In cases where a subject lacks the capacity for civil conduct or has limited capacity, written informed consent from their guardian must be obtained as per the law. If the subject is unable to read, an impartial witness should witness the entire informed consent process and sign and date the form. Subjects have the right to withdraw from the clinical trial at any stage.

Reduction and avoidance of bias

The imaging is adjudicated by an independent neuroimaging core laboratory, evaluating the diagnosis of ISR, sICAS and regional hypoperfusion. For the assessment of imaging results, two experienced neurointerventional physicians are required; in case of discrepancies, resolution is provided by a third independent neurointerventional physician. The NIHSS and mRS scores at each clinical trial centre are assessed by physicians independent of the operators. In order to reduce the bias of the trial results, the sponsor, the monitor and the leader of each trial centre train the investigators on the trial protocol before the start of the clinical trial so that the investigators can understand and be familiar with the investigational products. At the same time, all the new information about the investigational products found during the clinical trial should be mastered, and the doctors with rich experience in stent implantation should be selected. A monitoring plan is developed, with qualified monitors appointed by the sponsor, conducting regular on-site visits to trial hospitals. This is to ensure strict adherence to the study protocol, and scrutiny of case report forms/electronic data capture (EDC) is performed to confirm consistency with the original data.

Date management

The collection of test data is accomplished using an EDC system. A special scientific committee is established to design and manage the data. Each centre is responsible for collecting the data of enrolled patients at their centre. We appropriately protect patient privacy. Each patient is assigned an anonymous identification code. The case report form is filled out by the raters, handed over to the clinical monitor for review, submitted to an entry clerk for entry into the EDC system and finally logically checked by the data manager to ensure the authenticity and integrity of the data. All personnel involved in data collection receive professional training and assessment in advance on data collection to ensure the quality of data collection and management.

DISCUSSION

Advantages of the Xinwei drug-eluting stent (DES)

Xinwei DES is a self-expanding Nitinol DES specifically designed for treating sICAS. Previous research suggests that the use of drug-coated stents in sICAS treatment could help address issues such as ISR and stroke recurrence.[19 21 22 29] The NOVA study illustrates that DES can effectively reduce ISR and stroke recurrence in patients who have previously undergone bare stent implantation.[23] However, the application of balloon-expanded stents is limited and necessitates specific vascular conditions.[30] Different stent devices may be more appropriate for varying vascular pathways and pathological morphologies. Balloon-expanded stents and self-expanding stents each have their own set of advantages and disadvantages. Self-expanding stents offer enhanced flexibility, aiding in navigation through complex vascular access routes, while balloon-expanding stents provide greater radial force, leading to higher rates of successful revascularisation and lower residual stenosis.[31] Balloon-expanding stents are recommended for use in relatively straight blood vessel segments or areas with small diameter variations between distal and proximal blood vessels, short lengths of vascular stenosis and minimal perforating

vessels near vascular lesions.[32] On the other hand, patients with long vascular stenosis, severe vascular tortuosity, significant diameter differences between distal and proximal segments of blood vessels, and numerous perforating vessels near vascular lesions may benefit more from the application of Xinwei self-expanding DES. Compared with the Wingspan stent, the Xinwei DES offers suitable radial support force and uses a microcatheter for stent deployment, potentially enhancing the success rate of stent placement. Additionally, the Xinwei DES provides a wider range of stent sizes, making it suitable for thinner blood vessels or those with longer diseased segments. The surface of Xinwei DES is coated with PBMA to create a bottom coating that promotes the adhesion of epithelial cells on the scaffold, aiding in wound healing. The inclusion of rapamycin in the coating effectively hinders the growth and movement of smooth muscle cells, potentially lowering the risk of ISR.[16]

What are the differences in the inclusion criteria of this clinical trial?

Subgroup analysis of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis study reveals that among patients in the medical treatment group, those with watershed infarction and collateral circulation malcompensation have a 1-year stroke recurrence rate as high as 37%.[33] This indicates that endovascular therapy may offer greater benefits than medical therapy for high-risk subgroups. The study's inclusion criteria focus on patients with drug treatment failure and hypoperfusion due to target vascular lesions, aiming to demonstrate the potential advantages of Xinwei self-expanding DES in treating high-risk ICAS subgroups. Furthermore, patients with atherosclerotic plaque with high calcification should be excluded from consideration, considering the reduced radial support force of self-expanding stents and the limited penetration of rapamycin in heavily calcified plaques.

Why was superiority clinical trials design used in this study?

This prospective, multicentre, randomised controlled superiority clinical trial aims to assess the safety and effectiveness of the self-expanding DES (Xinwei intracranial DES system) in treating sICAS. The trial seeks to demonstrate that Xinwei DES is safer and more effective than the Wingspan stent. With a focus on evaluating the incidence of ISR 6 months postsurgery, the study involves 208 research subjects. Following the 6-month postoperative follow-up, a clinical summary report is prepared for product registration application. By comparing the efficacy of intracranial self-expanding DES and intracranial self-expanding BMS to treatment in patients with sICAS, this study aims to provide new evidence for sICAS treatment, potentially offering new therapeutic options on successful completion.

Limitations

This trial has several limitations. First, the experiment is conducted in China, and the included people are all Asians, which may limit the general applicability of the study results. Second, there is a lack of uniform standards for the use of assistive devices across centres. Additionally, the treatment randomisation is not blinded to the operators, treating physicians or patients. This trial compares the efficacy of self-expanding DES and self-expanding BMS for sICAS without comparing them to standard medical treatment.

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Contributors TL and YingkunH conceived of the study. YanyanH, JZ, LZ and ZW designed the study. ZZ contributed to the draft of the manuscript. WL, QD, SL, YP and YZ contributed to the revision of the manuscript. All authors read and approved the final manuscript. YingkunH is the guarantor.

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Competing interests None declared.

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Informed Consent Form (ICF)

Name of investigational medical device:	Intracranial drug-eluting stents
Specification/Model of investigational device:	HC*IDES-2013N-00, HC*IDES-2017N-00, HC*IDES-2020N-00, HC*IDES-3020N-00, HC*IDES-3025N-00, HC*IDES-3025M-00, HC*IDES-3030N-00, HC*IDES-3030M-00, HC*IDES-4020N-00, HC*IDES-4025N-00, HC*IDES-4025M-00, HC*IDES-4030N-00, HC*IDES-4030M-00, HC*IDES-4040N-00, HC*IDES-4040M-00, HC*IDES-5025N-00, HC*IDES-5025M-00, HC*IDES-5030N-00, HC*IDES-5030M-00, HC*IDES-5040N-00, HC*IDES-5040M-00, HC*IDES-2013N-12, HC*IDES-2017N-12, HC*IDES-2020N-12, HC*IDES-3020N-12, HC*IDES-3025N-12, HC*IDES-3025M-12, HC*IDES-3030N-12, HC*IDES-3030M-12, HC*IDES-4020N-12, HC*IDES-4025N-12, HC*IDES-4025M-12, HC*IDES-4030N-12, HC*IDES-4030M-12, HC*IDES-4040N-12, HC*IDES-4040M-12, HC*IDES-5025N-12, HC*IDES-5025M-12, HC*IDES-5030N-12, HC*IDES-5030M-12, HC*IDES-5040N-12, HC*IDES-5040M-12
Sponsor:	Shanghai HeartCare Medical Technology Co., Ltd
Agent:	Shanghai HeartCare Medical Technology Co., Ltd
Name of clinical trial protocol:	Evaluation of safety and efficacy of intracranial drug-eluting stents for symptomatic intracranial atherosclerotic stenosis: a prospective, multicenter, randomized controlled, superiority clinical trial
Clinical trial protocol No.:	SHXW-202301
ICF version No.:	V1.0
ICF version date:	2023-08-21

ICF version No.: V1.0 version date: 2023-08-21

Clinical trial institution: Henan Provincial People's Hospital

Principal investigator: Li Tianxiao

Distinguished sir/madam,

You are invited to participate in a clinical trial involving medical devices. The following describes the background, objectives, methods, potential benefits, risks or inconveniences, and your rights related to this trial. Please read this informed consent carefully before deciding to participate.

This informed consent provides information to help you decide whether to join this clinical trial. The lead institution for this trial is Henan Provincial People's Hospital, where the research is conducted under the supervision of Director Li Tianxiao from the Department of Cerebrovascular Diseases. If you have any questions, please ask the research physician responsible for this trial to ensure you fully understand the details. Your participation in this trial is based on voluntary principle. Please sign the statement in the informed consent form after reading the following data, if you participate in the clinical study of your own accord.

1. Study name, Objectives, and Background

1.1. Study name

Evaluation of safety and efficacy of intracranial drug-eluting stents for symptomatic intracranial atherosclerotic stenosis: a prospective, multicenter, randomized controlled, superiority clinical trial.

1.2. Objectives

To validate the safety and efficacy of intracranial drug-eluting stents manufactured by Shanghai HeartCare Medical Technology Co., Ltd in the treatment of symptomatic intracranial atherosclerotic stenosis.

1.3. Background

Intracranial atherosclerotic stenosis (ICAS) is a significant cause of ischemic stroke occurrence and recurrence worldwide. In North America, ICAS accounts for 8% to 10% of stroke etiologies, while in Asia, it constitutes 30% to 50%. In China, ICAS prevalence among stroke/transient ischemic attack (TIA) patients is as high as 46.6%.

Treatment options for intracranial atherosclerotic stenosis (ICAS) encompass medical therapy, surgical interventions, and endovascular procedures. Globally, surgical treatments, due to their higher complication rates, have not received widespread endorsement in guidelines. In contrast, medical and endovascular therapies continue to be investigated to establish the optimal approach for managing ICAS. Current evidence strongly supports medical therapy as the first-line treatment for ICAS. Notably, results from two pivotal randomized controlled trials (RCTs)—the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial in 2011 and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial in 2015—have consistently shown that aggressive medical therapy is both more effective and safer than endovascular interventions. Furthermore, a comprehensive review in 2018 comparing stent placement with aggressive medical therapy for symptomatic ICAS (sICAS) reaffirmed that medical therapy remains the preferred initial treatment option over endovascular procedures for managing sICAS.

The evolution of endovascular treatments for intracranial atherosclerotic stenosis (ICAS) reflects ongoing efforts to explore safer and more effective approaches, despite varying outcomes from pivotal studies such as SAMMPRIS, VISSIT, and the Chinese Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial, which did not establish the superiority of endovascular interventions over medical therapy alone. In real-world settings, due to persistent high risks of stroke recurrence under medical therapy, research continues to advance endovascular treatment methods, including material developments. Following SAMMPRIS, studies like the Wingspan Stent System Post-Market Surveillance (WEAVE) and multicenter registry data from China emphasize rigorous patient selection and refined procedural standards, highlighting improved safety and promising efficacy in treating sICAS at established neurointerventional centers. Insights from CASSISS underscore the ongoing focus on disease diagnosis, technological innovations, and advancements in interventional devices for future sICAS research.

Drug-eluting stents (DES) typically consist of a base layer and a drug-eluting

layer. The drug-eluting layer contains anti-proliferative drugs that are slowly released, inhibiting the proliferation and migration of vascular smooth muscle cells to prevent in-stent restenosis (ISR). Commonly used drugs in drug-eluting stents include paclitaxel and rapamycin. Theoretical considerations suggest that rapamycin-based drug-eluting stents may offer superior efficacy compared to paclitaxel-based ones. Paclitaxel, known for its cytotoxic properties, operates within a narrow therapeutic window, which poses a heightened risk of cytotoxic side effects due to its proximity to inhibitory and cytotoxic concentrations. In contrast, rapamycin, categorized as a cell inhibitor, features a broader therapeutic window between inhibitory and cytotoxic concentrations, thereby potentially enhancing safety relative to paclitaxel. Previous studies indicate that the use of drug-eluting stents or drug-coated balloons in endovascular interventions effectively mitigates ISR risk by suppressing neointimal proliferation. In China, institutions such as Xuanwu Hospital and Shanghai Changhai Hospital have achieved success rates exceeding 90% in treating intracranial atherosclerotic disease (ICAD) with drug-eluting stents. The primary intraoperative complication reported is branch occlusion, managed postoperatively with standard antiplatelet therapy. Notably, only one case reported ISR and symptomatic recurrence, with no instances of neurotoxic reactions; however, two cases experienced arterial aneurysm-like dilation. These findings underscore the technical feasibility of employing drug-eluting stents for patients with symptomatic ICAD resistant to rigorous medical treatment, leading to reduced ISR rates from 30% initially to 0-7% over the short term (6 months to 1 year). Importantly, most patients experiencing restenosis did not encounter stroke recurrence or drug-related neurotoxicity, underscoring the safety and efficacy of drug-eluting stents for ICAS treatment. Research focusing on coronary and carotid arteries suggests that drug-eluting stents may offer superior clinical and imaging outcomes compared to bare-metal stents for managing narrowings or ISR.

Based on the aforementioned points, drug-eluting stents have been validated for their safety and effectiveness in treating ICAS. Shanghai HeartCare Medical Technology Co., Ltd has independently developed an intracranial drug-eluting stent,

which has successfully undergone type testing at the National Medical Device Quality Supervision and Inspection Center in Tianjin, accredited by the State Administration of Drug Administration. It has received a favorable inspection report, confirming that the product design is finalized and meets the intended design specifications. Furthermore, the stent has undergone preclinical studies including animal experiments and risk-benefit analyses at Western Point Biotech (Chengdu) Co., Ltd., preliminarily demonstrating the safety and efficacy of this intracranial drug-eluting stent. With these achievements, the product is poised for clinical trials. There are plans in progress to initiate a prospective, multicenter, randomized controlled trial to assess the safety and effectiveness of the intracranial drug-eluting stent in treating symptomatic intracranial atherosclerotic stenosis.

2. Methods and Study Design

This study is a prospective, multicenter, randomized controlled superiority clinical trial to be conducted at multiple sites in China. The study aims to recruit 208 patients with symptomatic intracranial atherosclerotic stenosis (ICAS), with our center expecting to enroll 30 participants.

Participants or their guardians will sign an informed consent form (ICF) approved by the Ethics Committee. Eligible participants who meet the inclusion criteria and do not meet any exclusion criteria will be randomized using a central registration system. The intervention group will receive the intracranial drug-eluting stent manufactured by Shanghai HeartCare Medical Technology Co., Ltd., while the control group will be treated with the Wingspan Stent System produced by Stryker (Beijing) Medical Devices Co., Ltd. All participants will be followed up at the following intervals: during the surgery, within 7 days post-surgery or before discharge, at 30 days post-surgery, at 6 months, at 12 months, and at 24 months post-surgery.

The primary outcome measure is the incidence of in-stent restenosis (ISR) at 6 months post-surgery, which will be used to evaluate the safety and efficacy of the intracranial drug-eluting stent.

The study evaluated seven secondary outcomes: (1) success rate of device operation, which demonstrated successful stent implantation and coverage of the target lesion site, along with the successful withdrawal of the delivery system; (2) operation success rate, including successful stent implantation, absence of major adverse events during the procedure (such as death or stroke), and immediate postoperative residual stenosis < 50%; (3) in-stent restenosis rate at 12 months post-operation; (4) incidence of symptomatic stent restenosis at 6 months and 12 months post-operation; (5) Modified Rankin score (mRS) at 30 days, 6 months, and 12 months post-surgery; (6) National Institutes of Health Stroke Scale score (NIHSS) preoperatively and 6 months post-hospital discharge; (7) target lesion revascularization rates at 30 days, 6 months, and 12 months post-operation, defined as the need for any surgical or percutaneous intervention to restore blood supply to the target vessel. This study examines four safety indicators related to surgical outcomes: (1) stroke incidence at 30 days, 6 months, and 12 months post-surgery; (2) all-cause death rates at 30 days, 6 months, 12 months, and 24 months post-surgery; (3) incidence rates of device-related adverse events/serious adverse events at 30 days, 6 months, 12 months, and 24 months post-surgery; and (4) incidence rates of device defects. These measures will be used to verify the safety and efficacy of the intracranial drug-eluting stent manufactured by Shanghai HeartCare Medical Technology Co., Ltd., in treating symptomatic intracranial atherosclerotic stenosis. This study does not involve a central laboratory. All sample collection, utilization, and processing will be managed by our center.

3. Study Duration and Procedure

Your expected participation in this trial will last approximately 2 years, encompassing preoperative screening, surgery, and follow-up visits at 7 days post-surgery or before discharge, and at 30 days, 6 months, 12 months, and 24 months post-surgery.

4. Funding and Potential Conflicts of Interest

This trial is sponsored and funded by Shanghai HeartCare Medical Technology Co, Ltd. The researchers involved in this clinical trial do not own any equity (including shares) in Shanghai HeartCare Medical Technology Co., Ltd. or in companies that compete with its products. There are no conflicts of interest between Shanghai HeartCare Medical Technology Co., Ltd. and the researchers.

5. Potential Benefits

(1) Your intracranial atherosclerotic stenosis (ICAS) may be treated, potentially alleviating symptoms, improving your quality of life, and reducing the risk of disease recurrence.(2) Based on the randomization results, you will receive either the intracranial drug-eluting stent in the experimental group or the Wingspan Stent System (manufactured by Stryker (Beijing) Medical Devices Co., Ltd.) in the control group. Both stents will be provided free of charge by the sponsor.(3) You will receive professional medical care from doctors, along with close follow-up to guide your recovery.(4) By participating in this study, the medical data you provide may help other patients with similar conditions benefit in the future.

6. Potential Risks and Discomforts

Participation in this clinical trial and undergoing stent treatment carries potential risks similar to those associated with conventional stent implantation, including but not limited to:

Cerebrovascular perforator occlusion	Hypersensitivity and allergic reactions	Arrhythmias	Aneurysm
In-stent restenosis	Hyperperfusion syndrome	Poor stent apposition	Hypotension/Hypertension
Death	Failure to deliver the stent to the lesion site	Arterial dissection	Hemorrhage
Stroke	Infection and pain at the puncture site	Distal embolization	In-stent thrombosis
Fever	Pseudoaneurysm from femoral artery puncture	Adverse reactions to drugs, antiplatelet drugs, anticoagulants, or contrast agents	Thrombosis (acute, subacute, or late)
Thrombosis (acute, subacute, or late)	Hypercholesterolemia	Abnormal liver function tests	Arthralgia
Anemia	Diarrhea	Infection	Renal failure

Leukopenia	Thrombocytopenia	Hypercholesterolemia	Hypokalemia
Vascular occlusion	Vasospasm	Vascular perforation or rupture	/

Other unforeseen risks may also occur. If such situations arise, please promptly inform your research physician. They will provide proactive and comprehensive treatment to ensure your safety and rights.

Reproductive risks: Female participants who are breastfeeding or pregnant cannot participate in this trial. During the study period, if you become pregnant or suspect you are pregnant, it is crucial to inform the research physician immediately. If you plan to conceive within the next year, you should not participate in this trial. Participation may pose potential risks to sperm or eggs, potentially harming the child conceived during the study period. This harm has not been clinically confirmed and is unpredictable.

7. Treatment and Compensation for Trial-Related Injuries

If your health is compromised due to participation in this trial, please inform the research physician, who will take the necessary medical measures. According to Article 48 of the "Medical Device Clinical Trial Quality Management Regulations" of China, in the event of trial-related injuries, you are entitled to receive active treatment, and Shanghai HeartCare Medical Technology Co., Ltd will cover the medical expenses and provide economic compensation as stipulated by relevant laws.

Shanghai HeartCare Medical Technology Co., Ltd. has purchased insurance for this clinical trial. If you experience damage related to the trial, as judged by the researcher, they will provide active medical treatment. The insurance will offer appropriate compensation and indemnity. Any costs beyond the insurance coverage will be borne by the sponsor.

8. The treatment groups

Participants may be allocated to either the experimental group, receiving surgical treatment with the intracranial drug-eluting stent developed by Shanghai HeartCare

Medical Technology Co., Ltd. or the control group, receiving surgical treatment with the Wingspan Stent System from Stryker (Beijing) Medical Technology Co., Ltd.

9. Alternative Treatment Methods Outside of This Trial

If you choose not to participate in this clinical trial, you will not have access to the investigational medical devices used in this study. However, you still have the option to undergo surgical treatment using medical devices approved by the National Medical Products Administration (NMPA) for commercial use. Please note that you will be responsible for the costs associated with these devices.

Stent implantation is a recent emerging technology over the past 2-3 years. Apart from surgical treatment, pharmacotherapy is also a common clinical approach. You may opt for pharmacological treatment based on your condition, but specific treatment options should be discussed with your attending physician.

10. Confidentiality of Medical Records

The principal investigator is responsible for safeguarding your health, dignity, autonomy, and privacy, ensuring confidentiality of your personal information.

Your participation in the trial and your personal data collected during the trial are strictly confidential. The Ethics Committee, National Medical Products Administration, or the sponsor may access participant information as required by regulations, with a duty to maintain confidentiality. When the trial results are published, your personal identity or privacy will not be disclosed.

11. Free Medical Services and Other Related Benefits During the Trial

(1) After participating in this study, you will receive either the intracranial drug-eluting stent as determined by randomization or the control group treatment with the Wingspan Stent System (produced by Stryker (Beijing) Medical Device Co., Ltd.) provided free of charge by the sponsor.(2) During your participation in the study, various laboratory tests and examinations will be conducted, including routine tests such as complete blood count, blood biochemistry, coagulation function, as well as

head CTA, MRA, or DSA scans. These tests are part of standard care during surgical treatment, and even if you were not participating in the trial, they would generally be required for evaluation. The costs of these tests related to participation in the study will be covered by the sponsor (Results of the aforementioned tests conducted within the allowed preoperative period will not be repeated and will not be reimbursed if conducted before study participation). However, costs associated with treatments and tests required for other concurrent diseases are not covered.(3) If you are successfully enrolled in the study, follow-up imaging studies at 6 and 12 months post-surgery, including DSA or CTA scans, will be provided free of charge by the sponsor. Additionally, a subsidy of 1000 RMB for transportation and meals will be provided by the sponsor during each follow-up visit. This subsidy will be distributed uniformly upon completion of the 12-month follow-up based on the actual number of follow-up visits.

12. Voluntary Participation and Withdrawal from the Trial

You have the option to decline participation in this trial or withdraw at any time after informing the researcher without fear of discrimination or retaliation. Your medical treatment and rights will not be affected by your decision. If you require alternative diagnosis/treatment, fail to adhere to the trial protocol, or for any other valid reason, the researcher may terminate your continued participation in this trial.

You can learn about the progress related to the study at any time, and if you have any questions related to the study (e.g. rights and interests of the participant), or you have any discomfort or injury during the study, please contact (Investigator) _____at _____(Tel or mobile No.); and if you have any questions related to your rights and interests, contact the ethics committee of the Site at: _____.

Subject Informed Consent Statement

I have carefully read this informed consent form, and I have had the opportunity to ask questions, all of which have been answered to my satisfaction. I understand that participation in this trial is voluntary, and I may choose not to participate or withdraw at any time after informing the researcher, without fear of discrimination or retaliation. My medical treatment and rights will not be affected by this decision.

If I require alternative diagnosis/treatment, fail to adhere to the trial protocol, or for any other valid reason, the researcher may terminate my continued participation in this clinical trial.

I voluntarily consent to participate in this clinical trial, and I will receive a signed copy of the "Informed Consent Form."

Signature of the subject: _____ **Date:** _____

Tel: _____

Note: If the subject is unable to sign the informed consent form due to lack of capacity, their legal guardian or authorized representative should sign on their behalf.

Signature of guardian: _____ **Date:** _____

Relationship with subject: **Tel:** _____

Reason why the subject cannot sign: _____

Note: If the subject lacks reading ability, a notary or authorized witness will read the informed consent form and other pertinent information to them, witness the consent process, and sign the informed consent form on their behalf.

Signature of an impartial witness: **Date:** _____

Tel: _____

Statement of Investigator

I confirm that I have accurately informed the subject of the contents of the Informed Consent Form and answered the questions raised by the subject, and the subject is willing to participate in this clinical trial.

Signature of the Investigator: **Date:** _____

Tel: _____

The study involving human participants is reviewed and approved by the Ethics Committee of Drugs (Devices) Clinical Trials at Henan Provincial People's Hospital (reference number: AF/SC-08/05.0), the Ethics Committee of Clinical Trials at the First Affiliated Hospital of Harbin Medical University, the Ethics Committee of Clinical Trials at Tongji Hospital in Shanghai, the Ethics Committee of Clinical Trials at Xinxiang Central Hospital, the Ethics Committee of Clinical Trials at Hebei Provincial People's Hospital, the Ethics Committee of Clinical Trials at Anhui Provincial Hospital, the Ethics Committee of Clinical Trials at Linyi People's Hospital, the Ethics Committee of Clinical Trials at Jiangsu Provincial People's Hospital, the Ethics Committee of Clinical Trials at the First Affiliated Hospital of Zhejiang University School of Medicine, the Ethics Committee of Clinical Trials at Zhejiang Provincial People's Hospital, the Ethics Committee of Clinical Trials at Taizhou First People's Hospital, the Ethics Committee of Clinical Trials at Beijing Luhe Hospital, affiliated with Capital Medical University, the Ethics Committee of Clinical Trials at Peking University Third Hospital, the Ethics Committee of Clinical Trials at Liaoning Provincial People's Hospital, the Ethics Committee of Clinical Trials at the General Hospital of the Northern Theater Command of the People's Liberation Army, and the Ethics Committee of Clinical Trials at Benxi Central Hospital.