Protocol No.: 42CT (CN)

Clinical Trial to Evaluate the Safety and Efficacy of Absnow™ Absorbable ASD Closure System for ASD Patients

Name of investigational medical device: Absorbable ASD closure system

Product model & specification: Full specifications

Administrative category of investigational medical device: Class III medical device

Class III medical device requiring clinical trial examination and approval Yes □ No ■

Similar product in China Yes □ No ■

Protocol version No. and date: V1.4 - 02 December, 2019

Clinical trial leader: Guangdong Provincial People's Hospital

Coordinating investigator: Professor Zhiwei Zhang

Statistics Institution: Guangdong Cardiovascular Institute

Statistics director: Director He Li

Sponsor: Lifetech Scientific (Shenzhen) Co., Ltd.

Manufacturer: Lifetech Scientific (Shenzhen) Co., Ltd.

02 December, 2019

Filling instructions:

1. For a multicenter clinical trial, only the lead institution is written on the cover page, and other participating institutions are listed in the main body of the protocol.

2. For a multicenter clinical trial, only the principal investigator is written on the cover page.

Terms and Abbreviations

Number	Abbreviation	Definition
1	NMPA	National Medical Products Administration
2	ASD	Atrial Septal Defect
3	TTE	Transthoracic Echocardiography
4	TEE	Transesophageal Echocardiography
5	AE	Adverse Event
6	SAE	Serious Adverse Event
7	PLLA	Poly-L-lactic Acid
8	CHD	Congenital Heart Disease
9	IVC	Inferior Vena Cava
10	FDA	Food and Drug Administration
11	SOP	Standard Operating Procedure
12	DSA	Digital Subtraction Angiography
13	LOCF	Last Observation Carried Forward
14	FAS	Full Analysis Set
15	ITT	Intention to Treat
16	PPS	Per Protocol Set
17	SS	Safety Set
18	EDC	Electronic Data Capture System
19	CRF	Case Report Form
20	GCP	Good Clinical Practice
21	GMP	Good Manufacturing Practices
22	CT	Computed Tomography
23	OPC	Objective Performance Criteria

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Synopsis

Title of trial:	Clinical Trial to Evaluate the Safety and Efficacy of Absnow™ Absorbable ASD Closure System for ASD Patients
Sponsor	Lifetech Scientific (Shenzhen) Co., Ltd.
Device name	Absorbable ASD closure system
Administrative category	Class III medical device
Study design	(1) Objectives: To evaluate the safety and efficacy of Absnow™ absorbable closure system developed and produced by Lifetech Scientific (Shenzhen) Co., Ltd. for ASD patients; (2) This study is a prospective, multi-center, single-arm OPC clinical trial. It is planned to enroll 146 subjects to implant the closure system, carrying out 9 follow-up visits after the operation and recording the trial process of each subject in detail. (3) Primary safety endpoint: Rate of common complications during 360-day post operation; (4) Primary efficacy endpoint: Effective closure rate at 360-day post operation; (5) The interim report of the clinical trial will be completed after completing the 360-day follow-up post operation and obtaining corresponding clinical data and follow-up data. A registration application will be submitted to NMPA based on the interim report. (6) Before the national multi-center trial is officially launched, a pre-trial with a sample size of five cases (excluding from the overall effective sample size) will be conducted in Guangdong Provincial People's Hospital.
Indications	Patients with secundum ASD
Sample size	146 cases
Number of clinical trial institutions	11
Test time	(1) First patient in (FPI) date: Aug 2018 (2) Subject recruitment time: 6 months

	(3) Completion date of the 360-day follow-up visit of the last subject: March 2020
Efficacy evaluation	(1) Primary efficacy endpoint: effective closure rate at 360-day post operation (effective closure refers to no or only mild-small residual shunt in TTE or TEE observation after device implantation); (2) Secondary efficacy endpoint: immediate operation success rate (immediate operation success means that left and right disks are effectively fixed on left and right sides of atrial septum respectively and smoothly released without displacement or migration, and the delivery system is successfully withdrawn);
Safety evaluation	(1) Primary safety endpoint: Rate of common complications during 360-day post operation (refer to 7.1.7.1 of the main body for details) (2) Others safety endpoints: • Rate of device-related AEs; • Rate of SAEs;
Inclusion criteria (only those who meet all inclusion criteria can be enrolled)	(1) Age ≥ 3 years, body weight ≥ 10 kg; (2) Secundum left-to-right shunt ASD with hemodynamic significance; (3) Distance from the defect edge to coronary vein sinus, superior and inferior vena cava and pulmonary vein ≥ 5 mm; to atrioventricular valve ≥ 7 mm; (4) Atrial septum length (stretched diameter) > diameter of left disk.
Exclusion criteria (those who meet any of the exclusion criteria cannot be enrolled)	(1) Patients with primum, venous sinus and unroofed coronary sinus ASD; (2) Patients with atrial septal defect ≥ 26 mm; (3) Patients with other structural heart diseases in addition to ASD; (4) Patients with complication of obstructive pulmonary arterial hypertension or Eisenmenger syndrome; (5) Patients with infective endocarditis; (6) Patients with hemolysis, hemorrhagic disease or unhealed ulcer within 1 month before implantation, or any contraindication to aspirin treatment (except those who can take other antiplatelet agents for 6 consecutive months); (7) Patients with thrombosis (especially in left atrium or left auricle) as shown by echocardiography; (8) Patients with known hypercoagulable state;

	(9) Patients who have undergone heart surgery in the past; (10) Patients allergic to PLLA materials; (11) Patients refusing to sign the informed consent form; (12) Patients who have poor compliance with disease-related treatment and poor cooperation with follow-up visits; (13) Patients that are in pregnancy or lactation, or planned for pregnancy or get a positive pregnancy test result during the screening period; (14) Patients that have participated in any clinical trial that may affect the evaluation of the device in this trial and not completed or withdrawn from the previous clinical trial within 3 months prior to this trial screening period; (15) Patients not eligible for this clinical trial (determined by the investigator).
Device use specification	Apply the investigational devices to the subjects enrolled in the trial.
Statistical Analysis	(1) SAS 9.4 software will be used for statistical analysis; (2) This study adopts single-arm OPC design, and uses descriptive and inferential statistics for trial evaluation and statistical analysis; (3) Demographic and baseline data: Mean and standard deviation are used for calculation of age. Frequency and composition ratio are adopted for calculation of gender. Mean, standard deviation, median, the 25th and 75th quantiles, minimum and maximum values are adopted for the calculation of measurement data of vital signs. Frequency and composition ratio are used for the calculation of counting data of vital signs. Current medical history, past medical history, family history and concomitant medication history are described in list, and calculate the frequency and composition ratio as per classifications; (4) Analysis of laboratory tests: Mean, standard deviation, median, the 25th and 75th quantiles, minimum and maximum values are adopted for calculation of measurement data of laboratory tests such as blood routine, urine routine, liver and kidney function, coagulation function, myocardial enzyme, pregnancy test, etc. Whether they are within the normal medical reference ranges should be recorded and any test item with abnormal values of clinical significance should be listed; (5) ECG analysis: Frequency and composition ratio are calculated according to the types of arrhythmia; (6) Imaging analysis: Whether the occlusion is successful is determined by chest X-ray and

TTE. Frequency and composition ratio are calculated;

(7) Analysis of primary safety endpoint: Rate of common complications of Absnow™ absorbable ASD closure system during 360-day post operation and its 95% confidence interval (CI) are calculated;

(8) Analysis of primary efficacy endpoint: Effective closure rate of Absnow™ absorbable ASD closure system at 360-day post operation and its 95% CI are calculated;

(9) Analysis of other safety endpoints: Rates of device-related AEs and SAEs post operation are calculated, and SAE cases or trial termination due to AEs should be explained;

(10) Analysis of secondary efficacy endpoint: calculate the success rate of immediate process success;

(11) All statistical inferences are performed at a unilateral significance level of 0.025.

Main body

1. Sponsor

1.1 Name of sponsor

Lifetech Scientific (Shenzhen) Co., Ltd.

1.2 Sponsor address

Cybio electronic building, Langshan 2nd Street, North area of High-tech Park, Nanshan District, Shenzhen, Guangdong Province

Postcode: 518057, Tel: 0755-86026250

1.3 Contact information of sponsor

Contact person: Jingyu Lin, mobile phone: 18665696515

1.4 Social credit code of sponsor

91440300715217115L

2. List of participating institutions and investigators

Appendix 1 (any change of the list of participating institutions will be updated in the appendix rather than upgrading the version of the protocol)

3. Objectives and contents of clinical trial

3.1 Objectives

To evaluate the safety and efficacy of Absnow™ absorbable ASD closure system for ASD patients.

3.2 Contents

This clinical trial is a prospective study involving 146 subjects without a control group. Absnow™ absorbable ASD closure system will be used to treat ASD patients. Totally 9 follow-ups will be conducted within 5 years after operation. The rate of common complications during 360-day post operation is the primary safety endpoint, and the effective closure rate at 360-day post operation is the primary efficacy endpoint.

Before the national multi-center trial is officially launched, a pre-trial with a sample size of 5 cases (excluding from the overall effective sample size) will be conducted in Guangdong Provincial People's Hospital.

4. Background information

ASD is one of the common congenital heart diseases (CHD), which accounts for about 10% of pediatric CHDs. Surgery is the main treatment for ASD at first. Interventional therapy provides a new safe and effective treatment for CHD with its advantages of less trauma, confirmed efficacy, short recovery period and no need of cardiopulmonary bypass. A large number of clinical reports have shown that using interventional occluders to block ASD has a high success rate, good closure effect and low risk of complications.

At present, ASD occluders that are commonly applied for clinical use are double-sided umbrella-shaped structures woven by high-elastic nickel-titanium alloy wires. After reaching the clinical treatment effect, the occluders will continue to exist in the human body, which may cause a series of adverse events such as allergy and poisoning due to the increase of nickel ion concentration, and even induce cancer; Meanwhile, long-term existence of the occluder in vivo may lead to tissue wear, increased the risk of conduction block, and inability to receive occlusion of left atrial appendage.

The researchers of Lifetech Scientific (Shenzhen) Co., Ltd. (hereinafter referred to as Lifetech Scientific) have worked hard for many years to develop a novel Absnow™ absorbable ASD closure system. Its main raw material, poly-L-lactic acid (PLLA), is a degradable polymer material with good biocompatibility, which has been widely used in cardiovascular surgery, orthopedics and plastic surgery.

Absnow™ absorbable ASD closure system has been tested in animal models, with the operation success rate of 100%. After 6 months of observation, it was found that the myocardial cells and endothelial cells covered on the surface of the implanted device were not different from those of the control group (NiTi alloy occluder), while the inflammatory reaction was significantly lower than that of the control group. During the observation period, there was no device dislocation, migration, or obvious postoperative complications.

Absnow™ absorbable ASD closure system produced by Lifetech Scientific has passed the inspection of NMPA Shenzhen Medical Device Testing Center, which proves that the closure system meets the technical requirements of the product in terms of mechanical strength, physical and chemical properties, biological properties, etc. According to the requirements of the *Administrative Measures for Medical Device Registration* (Bureau Order No. 4) and the *Good Clinical Practice for Medical Devices* (Bureau Order No. 25) issued by NMPA, the product has been ready for clinical trials. Now Guangdong Provincial People's Hospital is taken as the lead institution to conduct this clinical trial to evaluate the safety and efficacy of Absnow™ absorbable ASD closure system developed and produced by Lifetech Scientific.

5. Investigational Product

5.1 Product features

The product can be recycled and repositioned repeatedly before being completely released, with simple operation, good closure effect, and good biocompatibility.

This product has a significant difference with the current nickel-titanium alloy occluders, which is the degradable PLLA polymer material (except for the markers). This material can be gradually degraded and absorbed by the human body after implantation, thus reducing the potential short- and medium-term complications after implantation, such as thromboembolism, friction injury, perforation, metal mesh breakage, and arrhythmia. At the same time, treatments for left heart disease are evolving, including percutaneous heart valve repair or replacement, arrhythmia research and treatment (e.g., pulmonary vein isolation and left atrial appendage closure), which often require access to the left atrium through the atrial septum. The implantation of conventional metal occluders prevents the establishment of the atrial septal access, while absorbable occluders avoid this problem.

5.2 Product description

5.2.1 Structural components

- Absnow™ absorbable ASD closure system structural components

The Absnow™ absorbable ASD Closure System (as known in Figure 1) consists of an absorbable ASD occlude (Figure 2) and a delivery system (Figure 3).

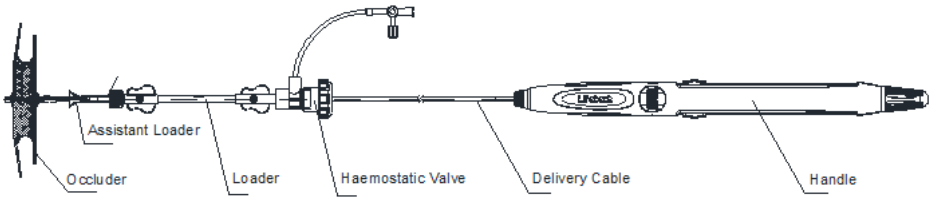


Figure 1. The Absnow™ absorbable ASD Closure System

- Absnow™ absorbable ASD occluder

As shown in Figure 2, the Absnow™ ASD occluder consists of a skeleton, a tip, a screw, sutures, membranes, a locker and markers. Biodegradable poly-L-lactide (PLLA) wire is shaped into two flat discs connected to each other with a waist that fits the size of the defect and three PLLA membranes are sewn within the two discs and the waist with PLLA sutures separately. Moreover, the occlude features a locker in aid of its shaping.

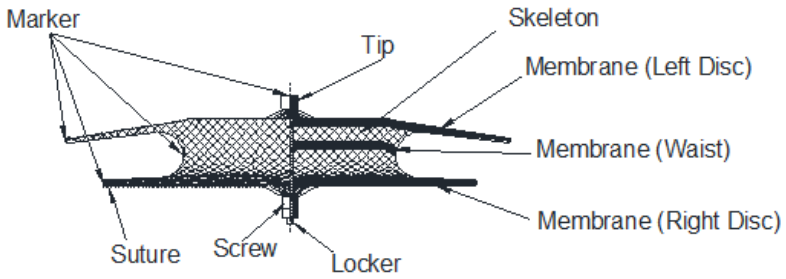


Figure 2. The Absnow™ ASD occluder

- Absnow™ absorbable ASD delivery system

As shown in Figure 3, the delivery system primarily consists of a delivery cable, a handle, a loader, a haemostatic valve and an assistant loader. The control handle includes the locking wheel, the push button and the back cover.

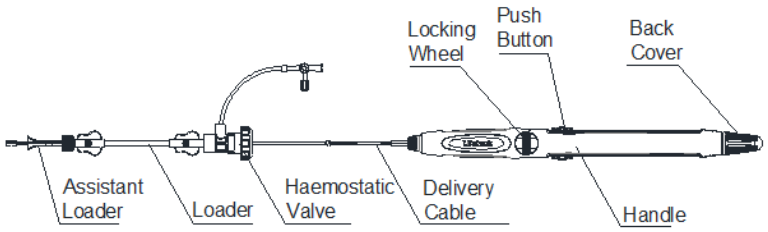


Figure 3. Delivery System of the Absnow™ ASD Closure System

The Absnow™ ASD Closure System shall be used in combination with the SteerEase™ Introducer manufactured by Lifetech.

5.2.2 Specifications

The specifications of the Absnow™ absorbable ASD Occluder are shown in Table 2.

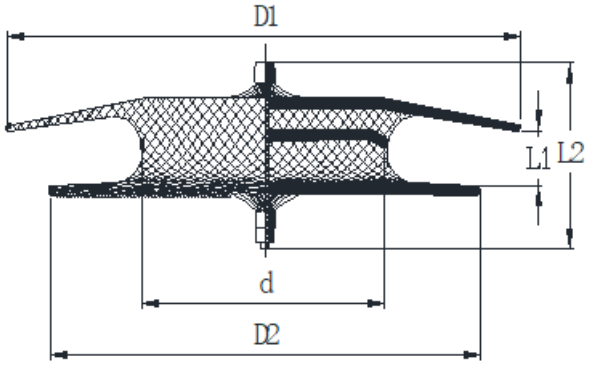


Figure 3. Illustration of Absnow™ ASD occluder

Table 2. Absnow™ ASD occluder and recommended delivery sheath sizes

Unit: mm

Device Specifications	Waist Diameter (d±1.5)	Left Disc Diameter (D1±2)	Right Disc Diameter (D2±2)	Distance between two Discs (L1)	Distance between Tip and Screw (L2)
LT-AASD-06	6	18	14	0≤L1≤6	14
LT-AASD-08	8	20	16	0≤L1≤6	14
LT-AASD-10	10	22	18	0≤L1≤6	14
LT-AASD-12	12	26	22	0≤L1≤6	14
LT-AASD-14	14	28	24	0≤L1≤6	14
LT-AASD-16	16	30	26	0≤L1≤6	14
LT-AASD-18	18	32	28	0≤L1≤6	15
LT-AASD-20	20	34	30	0≤L1≤6	15
LT-AASD-22	22	36	32	0≤L1≤6	15
LT-AASD-24	24	38	34	0≤L1≤6	15
LT-AASD-26	26	40	36	0≤L1≤6	15
LT-AASD-28	28	42	38	0≤L1≤6	15
LT-AASD-30	30	44	40	0≤L1≤6	16
LT-AASD-32	32	46	42	0≤L1≤6	16

5.2.3 Working mechanism

The Absnow™ absorbable ASD closure system works by contracting an umbrella occluder made of absorbable material into a sheath of corresponding specifications. Under the guidance of X-ray and echocardiography, the occluder is sent into the right atrium through the femoral vein and inferior vena cava, and then entre the left atrium through the atrial septal defect. Then, the left and right discs will be released in the left and right atria respectively, so that the waist of the occluder can be stuck in the defect position. The occluder will be fixed on the atrial septum to block blood shunts, providing conditions for the climbing and growth of new tissue cells, and achieving the purpose of treatment.

5.3 Investigation range

Patients with secundum ASD

6. Indications, contraindications and cautions

6.1 Indications

This product is suitable for patients with congenital heart disease secondary to groove ASD confirmed by clinical physical examination, chest X-ray and echocardiography, and meets the following conditions:

(1) Age ≥ 3 years, body weight ≥ 10 kg;

(2) Secundum left-to-right shunt ASD with hemodynamic significance;

(3) Distance from the defect edge to coronary vein sinus, superior and inferior vena cava and pulmonary vein ≥ 5 mm; to atrioventricular valve ≥ 7 mm;

(4) Atrial septum length (stretched diameter) > diameter of left disk.

6.2 Contraindications

(1) Patients of primum, venous sinus and unroofed coronary sinus ASD;

(2) Patients with atrial septal defect ≥ 26 mm;

(3) Patients with other structural heart diseases in addition to ASD;

(4) Patients with complication of obstructive pulmonary arterial hypertension or Eisenmenger syndrome;

(5) Patients with infective endocarditis;

(6) Patients with hemolysis, hemorrhagic disease or unhealed ulcer within 1 month before implantation, or any contraindication to aspirin treatment (except those who can take other antiplatelet agents for 6 consecutive months);

(7) Patients with thrombosis (especially in left atrium or left auricle) as shown by echocardiography;

(8) Patients allergic to PLLA materials.

6.3 Cautions

6.3.1 Patient selection

Some high-risk patients will have certain complications after the device implantation, such as device thrombosis. If this device is implanted in high-risk patients, it will require closer follow-up visits. High-risk patients include:

1) Device deformation at aortic root;

2) Defect of inferior vena cava (IVC) margin (risk of thrombosis).

6.3.2 Intraoperative and postoperative treatment recommendations

- Systemic heparinization should be performed throughout the operation process (100 U/kg for children and 3,000 U for adults);
- TTE or TEE should be used to assist the occluder placement;
- Aspirin (3-5 mg/(kg·d)) should be taken orally for 6 months after operation;
- Patients at risk of endocarditis should be given intramuscular injection of Benzathine Benzylpenicillin (1,200,000 U for adults and ≤ 600,000 U for children) once a month for 6 months.

7. Overall design

7.1 Study design

7.1.1 Study objectives

To evaluate whether the effective closure rate of absorbable ASD closure system at 360-day post operation is not lower than its OPC, and the rate of common complications during 360-day post operation is not higher than its OPC (see 8.2.1 total sample size for details).

7.1.2 Trial methods and selection basis

In this study, a prospective, multi-center and single-arm OPC design evaluation method is adopted.

(1) Prospective: a research method that uses the present as the starting point to follow up the future results. Prospective research results can provide evidence of causality and have unified diagnosis, detection and evaluation standards for the acquired data. Therefore, the data source and processing controllability are good;

(2) Multi-center: More than two clinical trial centers are selected to carry out the clinical trial. Using multi-center trial can obtain more cases within the same time period than single-center trial and shorten the overall clinical trial time. Multi-center trials are completed in different regions by different research centers and multiple clinical investigators. Therefore, the results and conclusions have good representation.

(3) Single-arm OPC design: Currently, the technique of ASD occlusion has been mature and widely applied to clinical use. Besides, a large number of clinical data, large-scale clinical trials, randomized controlled trials and systematic reviews (Meta analyses) of traditional metal products on the market have proved the safety and efficacy of this transcatheter occlusion (advantages compared with the open-heart surgery). In view of the fact that clinical trials of medical devices are often open-label studies, increased attention has been paid to non-randomized controlled designs in recent years. Among them, the single-arm OPC design is widely used in non-randomized controlled clinical trials of medical devices, which means that the single-arm OPC design can also evaluate the safety and efficacy of medical devices. For example, in the review of medical

devices by FDA, the application of single-arm OPC design in clinical trials of medical devices has been recognized. Lifetech Scientific (Shenzhen) Co., Ltd. has taken the lead in developing the ASD closure system with absorbable materials that have good biocompatibility in China. Its traditional metal material ASD closure systems have been sold in China and abroad for many years. The heart surgeons have rich interventional experience. The treatment has confirmed efficacy and the incidence of common complications is predictable. Traditional metal material products on the market, such as GORE® HELEX® Septal Occluder (NCT00581308), GORE® CARDIOFORM ASD Occluder (NCT02985684), AMPLATZER Septal Occluder (NCT00650936), all adopt single-arm OPC design to apply for FDA registration. Therefore, it is feasible to perform single-arm OPC design in this clinical trial.

7.1.3 Actions to reduce and avoid bias

(1) Before the start of the trial, the investigators should be trained uniformly to ensure that they fully know and understand the trial process and can operate the investigational device skillfully. The investigators must strictly follow the trial protocol during the trial. The clinical research associate should carry out quality control and monitoring to ensure that the investigators' operations and implementations are in strict accordance with the trial protocol. The above actions will be implemented in the whole implementation stage of the trial to reduce the gross errors or operation errors.

(2) The subjects will be screened strictly according to the inclusion and exclusion criteria of the trial protocol to ensure that the trial is carried out strictly according to the protocol.

(3) The efficacy and safety endpoints of the trial may be influenced by the proficiency and experience of the investigators. Therefore, participating investigators should have relevant treatment experiences, thus reducing the operation bias on the trial results.

(4) Data collation and management will be carried out after clinical trial completion. The data analyst will check and confirm the data issues through the data query table to avoid recording errors.

7.1.4 Device use specifications

SOP for key operations:

(1) Introduce the sheath tube and sheath core to the left superior pulmonary vein.

(2) Open the package and take out the ASD closure system.

(3) Soak the absorbable ASD closure system and loader in the physiological saline.

(4) Unscrew the locking wheel and push the pushing control forward to put the occluder into the guide sheath.

- Absorbable ASD closure system with specifications below 12: Push the push control to the first red dot and directly put the occluder into the guide sheath;
- Absorbable ASD closure system with specifications above 12: Push forward the pushing control to put part of the occluder into the sheath and repeat the above steps until the occluder is completely put into the guide sheath.

(5) Lock the locking wheel, hold the guide sheath with one hand, and pull the bell-mouth loader out of the guide sheath while rotating with the other hand;

(6) After complete exhaust, push the occluder into the delivery sheath and deliver it to the atrial septum along the delivery sheath;

(7) Place the distal end of the sheath at the pulmonary vein, and withdraw the sheath under DSA to expose all seven markers of the occluder. Adjust the position of sheath and occluder to locate the development site of waist at the atrial septal position. Unscrew the locking wheel, pull back the push control to the red dot in the middle, and partially release the left atrial disc, waist and part of the right atrial disc of the occluder.

(8) Carry out ultrasound to confirm that the two discs of the occluder are in the left and right atria respectively, then retract the push control, continue to shape the occluder, and keep the waist of the occluder straightly at the atrial septal position.

(9) When the push control is about two grids (10 mm) away from the last red dot, pull the steel cable slightly backward to make the left disk stick to the atrial septal position.

(10) Pull back the push control and push forward the steel cable at the same time until it is about one grid (5 mm) away from the last red dot and then stop pushing the push control. Carry out DSA to confirm that all seven markers have been displayed and TTE to confirm that the occluder is basically formed, the waist of the occluder is located at the atrial septum position, and the left and right atrial discs are close to the atrial septum positions on the left and right atrial sides respectively before tighten the locking wheel finally.

(11) Carry out ultrasound to examine the placement position, shape and residual shunt of the occluder;

(12) Unscrew the locking wheel and fasten the occluder. Carry out ultrasound to check the position, shape and residual shunt of the occluder.

(13) Release the occluder.

See the instruction for use (IFU) of the product for specific operation instructions and illustrations.

7.1.5 Selection of subjects

7.1.5.1 Inclusion criteria (only those who meet all the following criteria can be enrolled)

(1) Age ≥ 3 years, body weight ≥ 10 kg;

(2) Secundum left-to-right shunt ASD with hemodynamic significance;

(3) Distance from the defect edge to coronary vein sinus, superior and inferior vena cava and pulmonary vein ≥ 5 mm; to atrioventricular valve ≥ 7 mm;

(4) Atrial septum length (stretched diameter) > diameter of left disk.

7.1.5.2 Exclusion criteria (those who meet any of the following criteria cannot be enrolled)

(1) Patients of primum, venous sinus and unroofed coronary sinus ASD;

(2) Patients with atrial septal defect ≥26 mm;

(3) Patients with other structural heart diseases in addition to ASD;

(4) Patients with complication of obstructive pulmonary arterial hypertension or Eisenmenger syndrome;

(5) Patients with infective endocarditis;

(6) Patients with hemolysis, hemorrhagic disease or unhealed ulcer within 1 month before implantation, or any contraindication to aspirin treatment (except those who can take other antiplatelet agents for 6 consecutive months);

(7) Patients with thrombosis (especially in left atrium or left auricle) as shown by echocardiography;

(8) Patients with known hypercoagulable state;

(9) Patients who have undergone heart surgery in the past;

(10) Patients allergic to PLLA;

(11) Patients refusing to sign the informed consent form;

(12) Patients who have poor compliance with disease-related treatment and poor cooperation with follow-up visits;

(13) Patients that are in pregnancy or lactation, or planned for pregnancy or get a positive pregnancy test result during the screening period;

(14) Patients that have participated in any clinical trial that may affect the evaluation of the device in this trial and not completed or withdrawn from the previous clinical trial within 3 months prior to this trial screening period;

(15) Patients not eligible for this clinical trial (determined by the investigator).

7.1.5.3 Dropout Criteria and management

Subjects who have signed informed consent forms and are screened qualified quit the trial and fail to complete the observation period specified in the protocol are called dropout cases, regardless of when and why. The criteria for dropout are as follows:

(1) For whatever reason, the subject is unwilling or impossible to continue the clinical trial, and requires to withdraw from the clinical trial.

(2) Although the subject does not explicitly propose to withdraw from clinical trial, he/she no longer receive treatment and examination and loses to follow-up

(3) The subject presents SAE, and the investigator judges that the subject should withdraw from the clinical trial.

(4) The subject has poor compliance.

Dropout management: For all dropout cases, the summary form of clinical trial completion should be filled in the original records and the reasons for dropout should be analyzed. When the subject drops out, the investigator should contact the subject as much as possible, inquire the reason and record the last clinical symptom, and complete the evaluation items that can be achieved. If the subject withdraws from the trial due to AE, the investigator should take corresponding treatment actions according to the actual situation of the subject.

7.1.5.4 Trial termination criteria

Trial termination means that the clinical trial is not ended according to the protocol and discontinued halfway. The main purpose of termination is to protect the rights and interests of subjects and ensure the quality of trial. In addition to the Article 5 mentioned below, the sponsor and the investigators should jointly negotiate whether to terminate the trial:

(1) The trial should be terminated timely due to serious safety problems found during the trial;

(2) The trial should be terminated timely because the product is found to be of no clinical value during the trial;

(3) Major error is found in the protocol during the trial, which makes it difficult to evaluate the product safety and efficacy; Or serious deviation occurs during the implementation of the protocol and further continuation of the trial will make it difficult to evaluate the product safety and efficacy;

(4) Clinical trial institutions and investigators do not comply with the relevant laws and regulations of the clinical trial and the clinical trial protocol, which are not corrected after being pointed out, or are serious, or continue to be unchanged;

(5) National Medical Products Administration ordered the termination of clinical trial for some reasons.

From the perspective of protecting the rights and interests of the subjects, the investigators should continue to provide appropriate treatments for the subjects after the trial termination, and inform the subjects in detail of the management and related treatments received during the trial. The relevant data of the subjects can still be used to evaluate the safety of the product, and the termination of the trial should be timely fed back to the sponsor.

7.1.5.5 Enrollment time

It is estimated that the first subject will be enrolled in Aug 2018. Each clinical trial institution is expected to enroll three subjects every month, with a total time of six months for subject recruitment.

7.1.5.6 Expected clinical trial duration and determination basis

The total duration of this trial is five years and six months, and 146 subjects are planned to be enrolled within six months. After completing the 360-day visit data post operation, the interim statistical analysis report and the interim clinical trial report should be finished. And the registration application should be submitted to the NMPA. Then the follow-up of 2-5 years post operation will still be carried out continuously (once a year).

7.1.5.7 Expected duration of participation of each subject

According to the requirements of the trial protocol, each subject should receive screening before operation (-30 to 0 day), sign the informed consent form after passing the screening, undergo implantation of Absnow™ absorbable ASD closure system, and carry out visits before discharge, 30 days, 90 days, 180 days, 360 days, 2 years, 3 years, 4 years and 5 years post operation. Any AE/SAE found in the subject during clinical trial should be observed until the end or keeping stable.

7.1.5.8 Number of subjects required for clinical trial

Sample size: 146 cases

7.1.6 Efficacy evaluation method

7.1.6.1 Primary efficacy endpoint and corresponding evaluation, recording and analyzing method and time

Effective closure rate at 360-day post operation

Evaluation time: 360-day post operation

Definition of effective closure: no or only mild-small residual shunt (judging from left-to-right Doppler signal, left-to-right shunt signal with diameter < 5 mm) observed by TTE or TEE after device implantation.

Evaluation method: TEE or TTE

7.1.6.2 Secondary efficacy endpoint and corresponding evaluation, recording and analyzing method and time

Immediate operation success rate

Evaluation time: Immediately post operation

Immediate operation success means that left and right disks are effectively fixed on left and right sides of atrial septum respectively and smoothly released without displacement or migration and the delivery system is successfully withdrawn;

Note: the displacement and migration can be judged by observing whether the position of markers is the same as that before release under DSA, and whether the left and right discs are located on both sides of the atrial septum under TEE or TTE.

7.1.7 Safety endpoints and corresponding evaluation, recording and analyzing method and time:

7.1.7.1 Primary safety endpoint: Rate of common complications during 360-day post operation

Note: Common complications include (as shown in the following table)

SN.	Name	SN.	Name
1	Occluder displacement	5	Residual shunt above medium
2	High-grade atrioventricular block	6	Intractable headache or migraine
3	Cardiac tamponade	7	Cerebral embolism

4	Air embolism		

The definitions of common complications are as follows:

(1) Occluder displacement: refers to displacement of occluder to right atrium, right ventricular outflow tract, main pulmonary artery, left atrium, etc. due to special anatomical position of ASD, selection of too small occluder resulted from incorrect measurement and improper operation, etc.

(2) High-grade atrioventricular block: means that there are two or more continuous supraventricular excitations (generally sinus P waves) that cannot be transmitted down to the ventricle at an "appropriate" atrial rate (≤135 bpm), and this conduction barrier must be caused by block rather than interference induced by connection or ventricular ectopic pacing points.

(3) Cardiac tamponade: refers to cardiac compression, ventricular filling obstruction and a series of hemodynamic abnormalities, such as venous pressure increase and even cardiogenic shock, due to the rapid accumulation of fluid in pericardial cavity.

(4) Air embolism: refers to inadvertently injection of air into coronary artery due to improper operation of occluder implantation. Air embolism can temporarily block blood flow in coronary artery, which may lead to acute myocardial infarction, angina pectoris, arrhythmia and cardiac arrest.

(5) Residual shunt above medium: left-to-right shunt signal with diameter ≥5 mm, judging from Doppler left-to-right signal.

(6) Intractable headache or migraine: refers to the syndrome with recurrent headache as the main symptom, which may have aura and accompanying symptoms.

(7) Cerebral embolism: refers to various emboli (such as endocardial mural thrombus, atherosclerotic plaque, fat, etc.) that enter the cerebral artery with blood flow and block blood vessels, which will cause ischemic necrosis of brain tissue in the blood supply area of the artery and result in focal neurological deficit when collateral circulation cannot be compensated.

7.1.7.2 Other safety endpoints

(1) Rate of device-related AEs

Evaluation time: During the trial

Definition of device-related AE: refers to AE that is determined by the investigator to be related, possibly related, unlikely related to the device or the correlation between AE and device is unable to be judge. However, normal postoperative stress reactions, such as fever and constipation, should be distinguished, and those judged by investigators as normal postoperative stress reactions do not need to be recorded in adverse events.

(2) Rate of SAEs

Evaluation time: During the trial

Serious adverse events refer to events that cause death or serious deterioration of health, including fatal

diseases or injuries, permanent defects of body structure or body functions, hospitalization or prolonged hospital stay, and medical or surgical intervention to avoid causing permanent defects to the body structure or body functions; or that cause fetal distress, fetal death or congenital abnormalities, congenital defects, in the process of the clinical study.

7.1.8 Device deficiency and corresponding evaluation, recording and analyzing method and time:

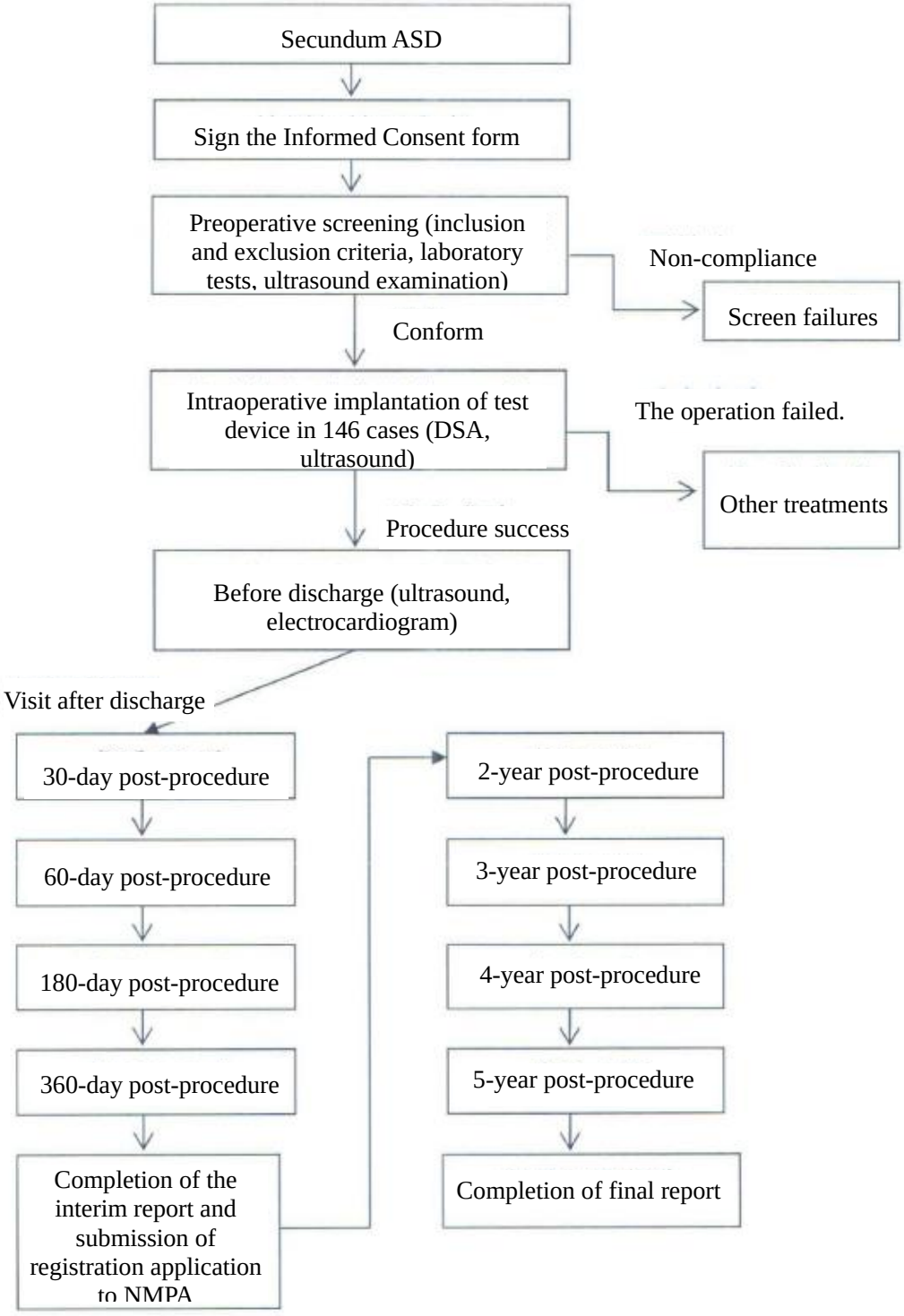
Rate of device deficiencies

Evaluation time: During the operation

Definition of device deficiency: refers to the deficiency of the investigational device which presents in the trial process, such as label error, plastic thread damage, ineffective fastening or release of the locking piece, displacement of shunt blocking membrane, etc.

7.2Trial process

7.2.1 Trial Flowchart


Secundum ASD
Sign the Informed Consent form
Preoperative screening (inclusion and exclusion criteria, laboratory tests, ultrasound examination)
Non-compliance
Screen failures
Conform
Intraoperative implantation of test device in 146 cases (DSA, ultrasound)
The operation failed.
Other treatments
Procedure success
Before discharge (ultrasound, electrocardiogram)
Visit after discharge
30-day post-procedure
60-day post-procedure
180-day post-procedure
360-day post-procedure
Completion of the interim report and submission of registration application to NMPA
2-year post-procedure
3-year post-procedure
4-year post-procedure
5-year post-procedure
Completion of final report

7.2.2 Data collecting summary

Number of visits / Visit item	Screening stage	Enrollment stage									
	Before operation	Intraoperative	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Observation cycle	-30～0d	0d	Before discharge	30±7d	90±14d	180±30d	360±30d	2y±60d	3y±60d	4y±60d	5y±60d
Informed consent form	▲										
Demographic data	▲										
Vital signs	▲		▲	▲	▲	▲	▲	▲	▲	▲	▲
Current medical history	▲										
Past history	▲										
Inclusion/exclusion criteria	▲										
Pregnancy test	▲										
Urine routine	▲										
Blood routine	▲		▲		▲	▲	▲	▲	▲		
Liver function	▲				▲	▲	▲	▲	▲		
Kidney function	▲				▲	▲	▲	▲	▲		
Cardiac enzymes	▲		▲		▲	▲	▲	▲	▲		
Coagulation function	▲										
TTE	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Chest X-ray	▲					▲	▲				
ECG	▲		▲	▲	▲	▲	▲	▲	▲	▲	▲
Medication record	▲	▲	▲	▲	▲	▲					

Common complications			▲	▲	▲	▲	▲				
AE			▲	▲	▲	▲	▲	▲	▲	▲	▲
Device deficiencies		▲									

7.2.3 Visit items

7.2.3.1 Medical history and vital signs

Demographic data, current medical history, past medical history and vital signs will be collected.

(1) Demographic data: sex, date of birth, height and weight

(2) Vital signs: blood pressure, pulse, body temperature and respiration

(3) Current medical history: symptom duration and admission time

(4) Past history: history of allergy, history of dysfunction of important organs (heart, lung, liver and kidney), and history of surgery

(5) Medication records: CRF only records anticoagulants, antiplatelets and antibiotics

7.2.3.2 Laboratory examination

The subjects must undergo complete laboratory tests before operation. The test items should include at least the following contents:

(1) Pregnancy test: applicable to women of reproductive age

(2) Urine routine: urine glucose (GLU), urine protein (PRO), urine red blood cell count (RBC), urine white blood cell count (WBC)

(3) Blood routine: hemoglobin (Hgb), white blood cell count (WBC), platelet count (PLT), neutrophil percentage (NEUT%)

(4) Liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT)

(5) Kidney function: serum creatinine (Scr), blood urea nitrogen (BUN)

(6) Cardiac enzymes: Creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH)

(7) Coagulation function: prothrombin time (PT), activated partial thromboplastin time (APTT), international standardized ratio (INR)

7.2.3.3 Electrocardiogram examination

(1) ECG

7.2.3.4 Imageological examinations

(1) Echocardiography

(2) Chest X-ray

7.2.4 Trial Flowchart

The subjects are required to carry out 9 visits before the end of the trial, specifically as follows:

7.2.4.1 Preoperative (-30 d - 0 d, outpatient/inpatient visit)

(1) Sign the Informed Consent form

(2) Demographic data

(3) Vital signs

(4) Current medical history

(5) Past history

(6) Screening according to the inclusion / exclusion criteria;

(7) Laboratory tests (pregnancy test, blood routine, coagulation function, urine routine, liver function, kidney function, cardiac enzymes)

(8) Echocardiography

(9) Chest X-ray

(10) ECG

(11) Medication record

7.2.4.2 Visit 1 (before discharge, hospitalization visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Cardiac enzymes)

(3) Echocardiography

(4) ECG

(5) Medication record

(6) Common complications

(7) AE

7.2.4.3 Visit 2 (30 ± 7 days post operation, outpatient visit)

(1) Vital signs

(2) Echocardiography

(3) ECG

(4) Medication record

(5) Common complications

(6) AE

7.2.4.4 Visit 3 (90 ± 14 days post operation, outpatient visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Liver function, Kidney function, Cardiac enzymes)

(3) Echocardiography

(4) ECG

(5) Medication record

(6) Common complications

(7) AE

7.2.4.5 Visit 4 (180 ± 30 days post operation, outpatient visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Liver function, Kidney function, Cardiac enzymes)

(3) Echocardiography

(4) Chest X-ray

(5) ECG

(6) Medication record

(7) Common complications

(8) AE

7.2.4.6 Visit 5 (360 ±30 days post operation, outpatient visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Liver function, Kidney function, Cardiac enzymes)

(3) Echocardiography

(4) Chest X-ray

(5) ECG

(6) Common complications

(7) AE

7.2.4.7 Visit 6 (2 years ± 60 days post operation, outpatient visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Liver function, Kidney function, Cardiac enzymes)

(3) Echocardiography

(4) ECG

(5) AE

7.2.4.8 Visit 7 (3 years ± 60 d post operation, outpatient visit)

(1) Vital signs

(2) Laboratory examination (Blood routine, Liver function, Kidney function, Cardiac enzymes)

(3) Echocardiography

(4) ECG

(5) AE

7.2.4.9 Visit 8 (4 years ± 60 d post operation, outpatient visit)

(1) Vital signs

(2) Echocardiography

(3) ECG

(4) AE

7.2.4.10 Visit 9 (5 years ± 60 d post operation, outpatient visit)

(1) Vital signs

(2) Echocardiography

(3) ECG

(4) AE

7.2.5 Medication guidance

(1) Postoperative heparin anticoagulation for 24 hours;

(2) Oral administration of Aspirin 3-5 mg/(kg.d) for children and 3 mg/(kg.d) for adults until 6 months post operation.

(3) Use of antibiotics within 30 min before operation.

7.3 Monitoring plan

According to the requirements of *Good Clinical Practice for Medical Devices*, the sponsor should select qualified clinical research associates to perform the monitoring duties on all participating institutions. The number of clinical research associates and the monitoring frequency depend on the complexity of clinical trial and the

number of participating institutions in the trial. The specific responsibilities include:

(1) Validate whether the clinical trial institution has proper conditions before the trial, including whether the staffing and training meet the requirements, whether the laboratory is fully equipped and in good working condition, and whether a sufficient number of subjects are expected, and whether the participating investigators are familiar with the trial requirements;

(2) Check whether the clinical trial institutions and investigators comply with relevant laws and regulations, *Good Clinical Practice for Medical Devices* and clinical trial protocol before, during and after the trial;

(3) Confirm whether each subject signs an informed consent form before participating in the clinical trial, and understand the selection of subjects and the progress of the trial. The visits, tests and examinations that the investigators fail to do, and whether mistakes and omissions are corrected, should be clearly and truthfully recorded. For revision of informed consent form, the affected subjects who have not finished the clinical trial process should be re-signed the form;

(4) Confirm that all case report forms are filled in correctly and consistent with the original data, and all errors or omissions have been corrected or noted, signed and dated by the investigators; Confirm and record the disease type, total number of cases, sex, age and therapeutic effect of each trial;

(5) Confirm that withdrawal from the clinical trial or failure to comply with the requirements of the informed consent form are recorded, and discuss such situations with the investigators;

(6) Confirm that all AEs, complications and other device defects are recorded, and SAEs and device defects that may lead to SAEs are reported and recorded within the specified time;

(7) Monitor the supply, use, maintenance, transportation, receiving, storage, distribution, processing and reclaiming of the test device;

(8) Monitor the regular maintenance and calibration of relevant equipment during clinical trial;

(9) Ensure that all clinical trial related documents received by investigators are the latest versions;

(10) A written report should be submitted to the sponsor after each monitoring. The report should include the name of the clinical research associates, date, time, place, contents, investigator name, project completion status, existing problems, conclusions and corrections to errors and omissions.

8. Statistical considerations

8.1Statistical design, methods and analysis procedures

The study is a prospective, multi-center and single-arm OPC design clinical trial. In this study, two primary endpoints are set, namely:

(1) Primary safety endpoint (low-priority index) -- Rate of common complications during 360-day post operation;

(2) Primary efficacy endpoint (high-priority index) -- Effective closure rate at 360-day post operation;

The two indexes in the trial are treated according to the co-primary endpoint. Only when both indexes reach the OPC can it be concluded that the investigational device meets the clinical application requirements.

8.2Sample size calculation

8.2.1 Total sample size

This clinical trial plans to recruit 146 subjects. The sample size determination process is as follows:

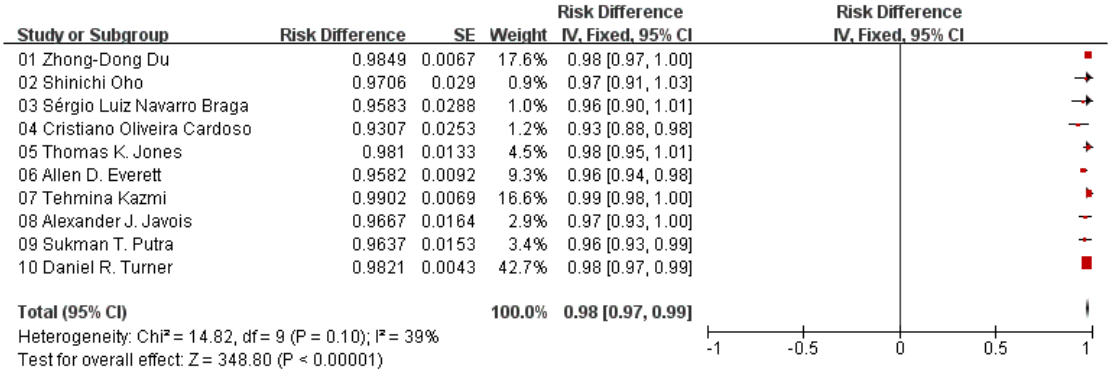
This clinical trial adopts single-arm OPC design and uses effective closure rate at 360-day post operation and the rate of common complications during 360-day post operation as the basis for sample size estimation.

At present, the technique of ASD occlusion is mature and widely used in clinic. A large number of clinical data, large-scale clinical trials, randomized controlled trials and systematic evaluations (Meta analyses) of traditional metal products on the market have proved the safety and efficacy of this treatment (advantages compared with the surgery). The literature data are shown in the table below.

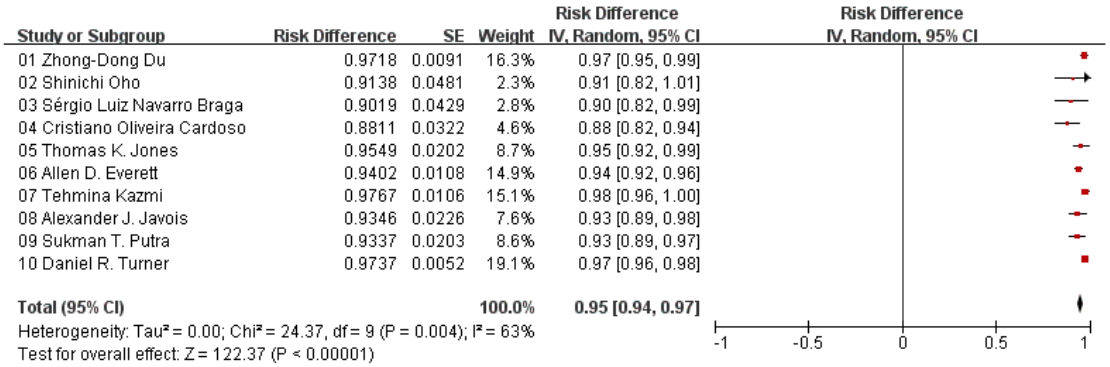
Literatures	Publishing date	Device name	Effective closure rate at 360-day post operation	Rate of common complications during 360-day post operation	Sample size
Zhong-Dong Du, et al. [1]	2002	Amplatzer Septal Occluder	98.5%	0.65%	288
Shinichi Oho, et al. [2]	2002	Amplatzer Septal Occluder	97%	2.86%	35
Sergio Luiz Navarro Braga, et al. [3]	2004	Amplatzer Septal Occluder	95.8%	4.1%	49
Cristiano Oliveira Cardoso, et al. [4]	2006	Amplatzer Septal Occluder	93%	3.96%	101
Thomas K. Jones, et al. [5]	2007	GORE HELEX Septal Occluder	98.1%	3.4%	119
Allen D. Everett, et al. [6]	2009	Amplatzer Septal Occluder	96%	0.9%	478
Tehmina Kazmi, et al. [7]	2009	Amplatzer Septal Occluder	99%	3.5%	204
Alexander J. Javois, et al. [8]	2014	GORE HELEX Septal Occluder	96.7%	--	137
Sukman T. Putra, et al. [9]	2015	Amplatzer Septal Occluder & Lifetech Heart ASD occluder	96.37%	2.6%	152
Daniel R. Turner, et al. [10]	2017	Amplatzer Septal Occluder	98.21%	1.6%	1000

1) Effective closure rate at 360-day post operation

Combining (Meta-analysis) of the one-year effective closure rates reported in each of the above documents shows that the one-year treatment success rate of the traditional metal ASD closure system is 98%, and the 95% CI is [97%, 99%].

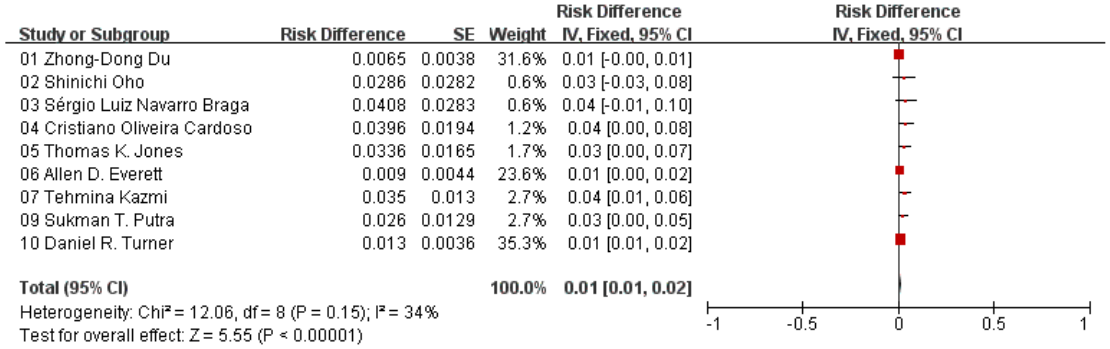


Combining (Meta-analysis) of the lower limits of 95% CI of one-year effective closure rates of each of the above documents shows that 95% CI of lower limits of 95% CI of one-year effective closure rates of traditional metal ASD closure system is [94%, 97%].

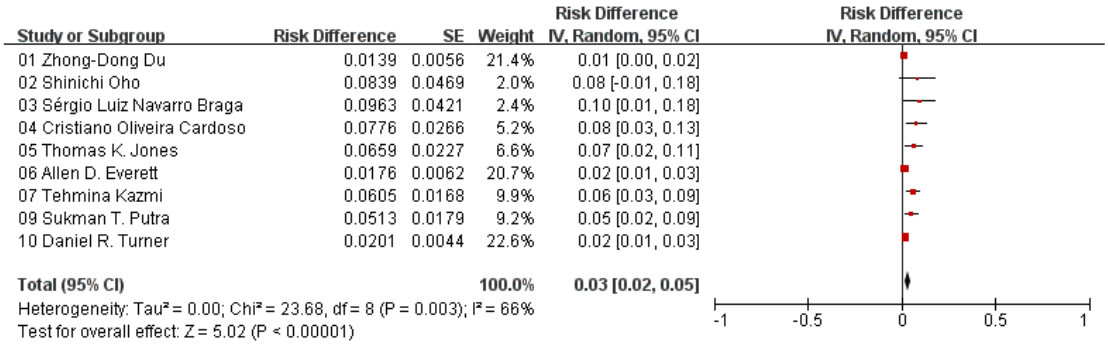


2) Rate of common complications during 360-day post operation

Combining (Meta-analysis) of the rates of common complications within one year reported in each of the above documents shows that the rate of common complications within one year is 1%, with a 95% CI of [1%, 2%].



Combining (Meta-analysis) of the upper limits of 95% CI of the rates of common complications in each of the above documents within one year shows that the 95% CI of the upper limits of 95% CI of the rate of common complications in the traditional metal ASD closure system within one year is [2%, 5%].



According to the summary of the results reported in the literatures, the treatment success rate at 360-day post operation of the ASD closure systems made of traditional metal materials ranged from 93% to 99%, and the rate of common complications during 360-day post operation was between 0.65% and 4.1%. Considering that the ASD closure systems made of traditional metal materials have been on the market for nearly 20 years, the industry has rich interventional experience and the treatment has confirmed efficacy and predictable incidences of common complications. In China, Lifetech Scientific has taken the lead in using absorbable materials that have good biocompatibility to develop novel ASD closure system and applied it for clinic use for the first time. At present, there is still no similar product on the market. Despite the relevant quality control measures, in multi-center clinical trials, there may still be differences in clinical practices (such as interventional techniques and evaluation experience) among different centers, resulting in different effects among different centers, especially the surgeon's learning curves, which will not only affect the proficiency of operations but also the efficacy of the investigational device and the prediction of common complications to a certain extent. In addition, we hope this study can make the clinical efficacy evaluation of the investigational device more realistic, fully understand the differences between the clinical practice of ASD occlusion with novel absorbable materials and the consensus of experts in the ASD occlusion with existing traditional metal occluders, provide objective comparative basis for clinical selection of novel absorbable ASD closure system, and also provide reference for the formulation and standardization of occlusion guidelines with novel absorbable materials in the future. Therefore, according to the results of meta analyses, clinical experience and primary endpoints defined in this trial after full discussion with clinical experts and statistical experts, the target and OPC of Absnow™ ASD closure system are set as follows:

Endpoints	Target	Unilateral boundary value of 95% CI (OPC)
Effective closure rate at 360-day post operation	99%	94%
Rate of common complications during 360-day post operation	1%	6%

Sample size is estimated by SAS9.4 software, and the operation is as follows:

a) Effective closure rate at 360-day post operation

```
proc power;
onesamplefreq
test = z
method = normal
nullproportion = 0.94
proportion = 0.99
sides = U
power = 0.8
alpha = 0.025
ntotal =. ;
run;
```

The POWER Procedure
Z Test for Binomial Proportion

Fixed Scenario Elements	
Method	Normal approximation
Number of Sides	U
Null Proportion	0.94
Alpha	0.025
Binomial Proportion	0.99
Nominal Power	0.8
Variance Estimate	Null Variance

Computed N Total	
Actual Power	N Total
0.802	121

The target and OPC of effective closure rate at 360-day post operation are set as 99% and 94%, respectively. SAS software calculation indicates that at least 121 patients are needed. Considering a dropout rate of 20%, 146 patients are required.

b) Rate of common complications during 360-day post operation

```
proc power;
onesamplefreq
test = z
method = normal
nullproportion = 0.06
proportion = 0.01
sides = L
power = 0.8
alpha = 0.025
ntotal = .;
run;
```

The POWER Procedure
Z Test for Binomial Proportion

Fixed Scenario Elements	
Method	Normal approximation
Number of Sides	L
Null Proportion	0.06
Alpha	0.025
Binomial Proportion	0.01
Nominal Power	0.8
Variance Estimate	Null Variance

Computed N Total	
Actual Power	N Total
0.802	121

The target and OPC of rate of common complications during 360-day post operation are set as 1% and 6%, respectively. SAS software calculation indicates that at least 121 patients are needed. Considering a dropout rate of 20%, 146 patients are required.

8.2.2 Number of clinical trial subjects of each disease and determination basis

In this clinical trial, congenital heart disease patients with secundum ASD who need to be implanted with occluder were taken as subjects to evaluate the safety and efficacy of Absnow™ absorbable ASD closure system. The number of clinical trial subjects of various diseases is not involved.

8.2.3 Minimum and maximum number of subjects in each clinical trial institution and determination basis

This clinical trial plans to recruit 146 subjects, and it is estimated that 11 clinical trial institutions (centers) will participate in this trial. The samples in each center will be balanced during the trial. Combined with the total sample size, the number of participating clinical trial institutions, and considering the different number of disease sources in each center, each clinical trial institution (center) can recruit no more than 50% of subjects at most.

8.3Significance level and power

This trial adopts single-arm design and the significance level α (one-sided) = 0.025, and the power is 80%.

8.4Expected dropout rate

(1) Dropout refers to the early withdrawal of the subjects during the clinical trial because of various reasons. For example, patients voluntarily withdraw the informed consent, lose follow-up and cannot complete the whole process of clinical trials due to AEs.

(2) In the process of sample size estimation, the expected maximum dropout rate is set at 20%, which refers to the proportion of dropout cases.

8.5Qualified/unqualified criteria for clinical trial results

The rate of common complications during 360-day post operation and the effective closure rate at 360-day post operation are calculated. If the upper bound of the 95% CI is less than 6% of the preset target value and the lower bound of the 95% CI is greater than the preset target value of 94%, it can be considered that the safety and efficacy of Absnow™ absorbable ASD closure system meet the criteria. The two indicators are treated according to the co-primary endpoint. It can be concluded that the investigational device meets the clinical application requirements only when both indicators reach the OPC

8.6Criteria and reason for trial termination based on statistics

(1) This clinical trial plans to conduct an interim effect evaluation. All subjects will not receive further interventions after the device is implanted. An interim evaluation on the safety and efficacy will be conducted after the 360-day follow-up data post operation are obtained.

(2) The results of interim effect evaluation do not affect the subsequent follow-ups (visits 6, 7, 8 and 9) and the final statistical analysis after the completion of the trial. Therefore, there is no need to set the criteria and reasons for trial termination.

8.7Data processing methods

8.7.4 Data statistical methods

(1) SAS9.4 software is used for the statistical analysis;

(2) This study adopts a single-arm OPC design, and uses descriptive statistics and inferential statistics for trial evaluation and statistical analysis;

(3) Demographic and baseline data: Mean and standard deviation are used for calculation of age. Frequency and composition ratio are adopted for calculation of gender. Mean, standard deviation, median, the 25^{th} and 75^{th} quantiles, minimum and maximum values are adopted for the calculation of continuous variables of vital signs. Frequency and composition ratio are used for the calculation of discrete variables of vital signs. Current medical history, past medical history, family history and concomitant medication history are described in list, and the frequency and composition ratio are used for calculation as per classification;

(4) Analysis of laboratory tests: Mean, standard deviation, median, the 25^{th} and 75^{th} quantiles, minimum and maximum values are adopted for calculation of continuous variables of laboratory tests such as blood routine, urine routine, liver and kidney function, coagulation function, myocardial enzyme, pregnancy test, etc. Whether they are within the normal medical reference ranges should be recorded and any test item with abnormal values of clinical significance should be listed;

(5) ECG analysis: Frequency and composition ratio are calculated according to the types of arrhythmia;

(6) Imaging analysis: Whether the occlusion is successful is determined by chest X-ray and TTE. Frequency and composition ratio are calculated;

(7) Analysis of primary safety endpoint: Rate of common complications of absorbable ASD closure system during 360-day post operation and its 95% CI are calculated;

(8) Analysis of primary efficacy endpoint: Effective closure rate of Absnow™ absorbable ASD closure system at 360-day post operation and its 95% CI are calculated;

(9) Analysis of other safety endpoints: Rates of device-related AEs and SAEs are calculated after operation, and explanations for trial termination due to AEs and SAEs occurred should be provided;

(10) Analysis of secondary efficacy endpoint: Immediate operation success rate is calculated;

(11) All statistical inferences are carried out at unilateral and significance level of 0.025.

8.7.2 Missing and unreasonable data

The trial should ensure that the data records are 100% correct, especially the primary endpoints. For missing, unused and irrational data or data of withdrawal subjects, strict review should be conducted. The basic statistical principles for processing these data are as follows:

(1) The details of each dropout subject will be described;

(2) The last observation carried forward (LOCF) method will be applied for the missing values of the main evaluation indicators;

(3) The missing values of qualitative or quantitative secondary endpoints are not carried forward, and are

handled according to the missing values;

(4) The missing values of all safety endpoints are not carried forward, and are handled according to the missing values.

8.8Statistical analysis plan deviation

In principle, only the contents of the statistical analysis plan according to the established protocol can be demonstrated in the clinical trial report. In case of other situations, a meeting will be held to discuss with the principal investigator and experts, and then whether to modify the statistical analysis plan will be decided according to their opinions.

8.9Subject selection criteria and reasons

(1) Full analysis set (FAS): According to the basic principles of Intention to Treat (ITT), FAS refers to the set of subjects that comply with the ITT principles. It includes:

a) Subjects who have been treated with the investigational device, achieved the immediate operation success, and have at least one observation data of primary endpoints after baseline;

b) Subjects who have received treatment with the investigational device, but have failed in the implantation because of the device itself, regardless of whether there is test device in the body.

If the implantation is abandoned due to other clinical reasons and there is no investigational device in the body, such subjects will not be included in the FAS. The definition of receiving the investigational device treatment is that if any part of the device, including the occluder itself and its delivery device, contact with human body through vascular approach, it can be considered as receiving the device treatment. FAS will be the main data set for baseline data analysis, primary safety and efficacy evaluation.

(2) Per protocol set (PPS): refers to subjects who have no serious violation of the study protocol in FAS, have good compliance, have not used drugs or treatments that may affect the efficacy evaluation during the trial, and have no missing data of primary endpoints. Unless otherwise specified, no carrying forward will be performed for the missing data of PPS. Theoretically, PPS should exclude subjects who have not completed all the visit plans due to various reasons, except that whether the subject's ASD has been successfully treated can be judged according to the existing results. PPS will be the secondary data set for efficacy evaluation.

(3) Safety set (SS): It is used for safety evaluation of the clinical trial, including all subjects who have been treated with the device at least once. SS will be the main data set of safety analysis.

(4) The efficacy evaluation of the device is mainly based on FAS, and PPS is only used as a reference data set for efficacy evaluation. Safety evaluation is based on SS. According to the above criteria, the subjects will be included in FAS, PPS and SS for interim efficacy evaluation and analysis at 360-day post operation. In the fifth year after operation, the subjects will be also included in FAS, PPS and SS for finally efficacy evaluation

and analysis according to the above criteria.

9. Data Management

9.1 Database design

(1) Electronic data capture (EDC) system is used to establish the database for this clinical trial.

(2) CRF designers will annotate the final version of the blank CRF form, and describe in detail the necessary elements such as variable name, length, type and value domain of database variables.

(3) The database designer will determine the database creation requirements and the database structure according to the CRF and its annotation, and then design the database.

(4) The database must be thoroughly tested to ensure that the content and structure of the database are consistent with CRF and annotated CRF, the specified data (variables) can be properly entered into the database, and the entered data can be correctly exported to the corresponding database variables.

9.2 Data reception and data entry

(1) EDC system is used to establish the database for this clinical trial, and eCRF is adopted to save and transmit the trial information of the subjects. EDC is strictly protected by password, and only those who directly participate in the research can obtain EDC account number. The authorized staff are responsible for inputting the trial data into EDC.

(2) Before data entry, the data administrator trains the entry staff or investigator on system operation or special items of this study.

(3) After the data entry starts, the entry staff or investigator should enter the data according to the EDC operation guideline and the EDC entry instructions of this project. Data modification caused by entry errors or other reasons will be recorded on EDC and confirmed by investigators. The CRA should check the data in the database with the original data to ensure that they are consistent. The entered eCRF should be signed by the investigators electronically.

9.3 Data audit and data query management

(1) Data audit includes manual data check, and program audit designed to identify wrong and invalid data range, data integrity, protocol violation and consistency check. The data administrator should complete the writing, approval and other related processes of the data audit plan before the enrollment of the first subject, and determine the data audit contents. The programmer should program and test the audit program according to the finalized data audit plan.

(2) According to the results of manual inspection and program audit, the data administrator will solve the

questionable data in the form of data query table, data processing agreement and self-evident correction, and update the database according to the answers or descriptions of relevant documents.

9.4Database locking and data archiving

(1) The clinical trial database must be closed and locked to ensure the consistency and integrity of data results, data analysis and data submitted to authorities.

(2) When all the data have been received and all data sorting has been completed, all queries have been answered, all unanswered questions have been clarified, the data review report has been validated, the statistical analysis data sets have been clearly divided, and the data quality control has been completed (database quality reaches the standard), the data administrator submits a database lock application to the project team members. After joint confirmation by the investigator, the sponsor and the project team members, the data editing permission of the database is recovered, and the database is locked. Then the data administrator shall timely transmit the data to the statistical analysis department. If data correction is required, the review, approval and other related processes of the database unlocking application form shall be completed to unlock the database, so that the corresponding personnel can enter the database to correct the data.

(3) The data administrator shall establish a data management project folder. When data or record files meet the archiving conditions, the data administrator is responsible for archiving them. When the study is completed, the data administrator revokes the relevant personnel's database access permissions, creates a copy of the database, and archives study documents and data management documents.

10. Feasibility analysis

10.1 Analysis of the likelihood of success

(1) Relevant clinical trials and post-marketing data reports have proved that metal ASD occluder is safe and reliable. Moreover, this kind of products have been reported in clinical use for many years, and their safety and efficacy have been verified;

(2) The company that produces this device has rich experience, and the product quality meets the requirements of the clinical trial. The device has passed the product registration inspection designated by NMPA in China;

(3) The clinical institutions undertaking this trial all have complete instruments, equipment and technical resources;

(4) The investigators are outstanding academic leaders in the field of interventional therapy for children with congenital heart disease in China. They are physicians with rich experience in clinical trials, have participated in GCP and related trainings, and can treat the subjects in strict accordance with the clinical

trial protocol.

10.2 Analysis of the likelihood of failure

(1) There are too many subjects who quit the trial due to SAEs;

(2) Subjects who lose to follow-up account for more than 20% of the sample size;

(3) IFU and labeling information of the device cannot effectively guide the operator;

(4) Serious safety problems are found during the trial;

(5) Major mistakes are found in the protocol during the trial, leading to difficulty in evaluating the product efficacy;

(6) The operation of the trial personnel is unskilled.

10.3 Conclusion

In conclusion, this device can benefit patients with secundum ASD. This trial is feasible and has a great possibility of success.

11. Quality control of clinical trial

11.1 Quality Assurance

11.1.1 Definition

It refers to planned and systematic activities. The purpose of establishing these activities is to ensure the research, generation, citation (recording) and reporting of data according to the requirements of *Good Clinical Practice for Medical Devices* and corresponding laws and regulations.

11.1.2 Audit

It refers to the systematic and independent inspection of activities and documents related to clinical trials organized by the sponsor to determine whether the implementation of such activities, data recording, analysis and reporting conform to the clinical trial protocol, SOPs, *Good Clinical Practice for Medical Devices* and relevant applicable management requirements.

11.1.3 Inspection

It refers to the activities of the drug regulatory agencies to review, supervise and manage the relevant documents, facilities, records and other aspects of a clinical trial.

11.1.4 Clinical trial monitoring

(1) The sponsor is responsible for comprehensively tracking and auditing the implementation of clinical trial,

ensuring that the trial comply with the *Good Clinical Practice for Medical Devices* and relevant laws and regulations, and follow the implementation of the trial protocol. NMPA may also inspect the clinical trial during or after the trial. If investigators receive such notices, they should inform the sponsor in time. The CRA will carry out regular visits to monitor the progress and completion of the trial.

(2) The CRA will check the completeness of the case records, the accuracy of the contents of the case report form, verify the trial data, and check the compliance of the investigators with the trial protocol and the *Good Clinical Practice for Medical Devices*, and ensure the accuracy of the distribution, storage and counting of investigational devices.

11.2 Quality control

11.2.1 Definition

It is defined as operating techniques and activities under the quality assurance system, such as monitoring. The purpose of quality control is to verify that the quality of research-related activities meets the requirements. Quality control should be applied to every stage of data processing to ensure that all data are credible and correctly processed.

11.2.2 Research monitoring

Authorized and qualified CRA will visit the clinical trial institutions regularly according to the monitoring plan, check the original data, verify the compliance of the investigators with the protocol and regulations, and assist the investigators.

11.2.3 Laboratory quality control

Each clinical center laboratory should establish standard operating procedures and quality control procedures, and each laboratory test item must adopt the national legal measurement unit. The test report items must be complete (including date, test items, test results and normal ranges) with signatures of the relevant personnel. Special test items must be specially tested by the special personnel.

11.2.4 Qualifications of investigators

The participating investigators of the clinical trial must have professional specialties, qualification and ability for the clinical trial. The staff should be relatively stable after the qualification inspection is approved.

11.2.5 Pre-trial training of investigators

The sponsor is responsible for the training of investigators before the start of the trial, so as to help the clinical trial personnel fully understand and know the overall situation, protocol and CRF.

12. Ethical issues and informed consent

12.1 Ethical considerations

(1) This clinical trial must follow the Declaration of Helsinki and the relevant medical device clinical trial norms and regulations in China. Before the start of the study, the protocol must be approved by the ethics committee (EC) of the institutions.

(2) Before each subject is selected for this study, the investigators have the responsibility to explain the study content to the subject in oral or written language in a way that the subject can understand, and to answer the subject's questions seriously. Before enrollment, each subject must be given a written subject informed consent form. It is the responsibility of the investigators to obtain the informed consent form before each subject enters the study and keep it in the study files.

(3) The basis of this trial includes the *Declaration of Helsinki*, *Good Manufacturing Practices (GMP) of Medical Devices, ICH-GCP* and relevant laws and regulations applicable to the People's Republic of China.

(4) Based on ethical considerations, ICH-GCP and relevant laws and regulations applicable to the People's Republic of China, preclinical tests of the investigational device are required before the clinical use. The design and implementation of this trial have put the safety of the subjects first. Therefore, in the preclinical tests, the biological safety of the materials used should be firstly detected to minimize the potential risks when using the materials. In order to clarify the security problem fundamentally, various standards of this trial have also been determined.

12.2 Protocol approval

Before clinical trial, the investigator shall submit the study protocol, informed consent form and other related documents to the medical ethics committee of the hospital which the clinical trial institution belongs to. The clinical trial can be started only after obtaining the approval of the ethics committee. Any modification of the study protocol must be approved by the ethics committee before implementation.

12.3 Informed consent

(1) Before each subject is enrolled for this study, the investigator is responsible for fully and comprehensively introducing the contents and instructions of the informed consent form to the subject or his/her guardian in written form, which must include the following contents:

1) Objective and description of the trial;

2) Procedures, time limit and examination operation of the trial;

3) Any foreseeable danger and discomfort to the subject;

4) Possible risks and expected benefits;

5) The subjects have the right to withdraw from the trial at any stage without discrimination or retaliation;

6) Other treatment actions that can be taken;

7) Confidentiality of subject data;

8) Subject compensation;

9) Contact information of the investigator;

10) Contact information of the ethics committee.

(2) The informed consent form should be written in a language that the subject or guardian can understand. Informed consent form should not contain any content that will cause the subjects to give up their legitimate rights and interests and exempt the clinical trial institutions and investigators, the sponsors or their agents from being responsible.

(3) Before enrollment, each subject must be given a written informed consent form. The investigator is responsible for obtaining informed consent form before each subject enters the study and keeping it in the study archives.

(4) For incapacitated subjects, if the ethics committee agrees in principle and investigators think that participating in clinical trial conforms to own interests of the subjects, they can also be enrolled in this clinical trial, but their guardian should sign with date before the trial.

(5) If a subject and his/her guardian both are incapable of reading, a witness shall be present during the consent process. After explaining the consent form in detail and ensuring the oral informed consent is consistent with the written informed consent form, the subject or his/her guardian gives oral consent, and the witness signs and dates the informed consent form. The witness's signature and the investigator's signature shall be on the same day.

(6) Because this trial involves minors, according to relevant laws and regulations, people aged 3-13, 14-17 and over 18 belong to children, teenagers and adults, respectively. Minors aged over 8 must sign corresponding informed consent forms and obtain the informed consent forms of their parents or guardians; Minors aged 3 - 8 only need to obtain the informed consent forms of their parents or guardians. (Refer to the document *Technical Guidelines for Drug Clinical Trials in Pediatric Populations* and *General Principles of Civil Law* newly revised in 2017)

(7) Please refer to informed consent form for details of informed consent.

12.4 Personal data and data protection

(1) All data obtained in clinical trial are subject to data protection. The investigator shall not disclose the subjects' name and other personal information (excluding date of birth/age and gender).

(2) The CRF and other documents transmitted to the sponsor do not contain names, but only the subject's study code. Similarly, statistical evaluation of data can only be performed under the subject's study code. Only the investigator can identify the subject's name and other personal information via the study code.

(3) If a subject need to be identified by his/her name due to medical reasons during the study process, all

relevant personnel are obliged to keep it confidential.

13. AEs and device deficiencies

13.1 Definition of adverse event

AE refers to adverse medical events occurs during clinical trials, whether related to the test medical devices or not. The possible AEs in this study include: (1) common complications; (2) Expected or unexpected SAE; (3) Expected or unexpected AE

13.1.1 Grading of adverse events

Grade refers to the severity of the AE. CTCAE (Version 5.0, released on 27-Jul-2017) displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following basic criteria:

CTCAE grading

Grade	**Clinical description**
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.
Remarks	A semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Activities of Daily Living (ADL): * Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.2 Report and handling of AEs

All AEs observed during the trial must be truthfully recorded in the adverse event form. Investigator should carry out targeted treatment and follow-up to AEs until symptoms disappear or become stable.

13.1.3 Determination of the relationship between AE and test product and operation

The subject should evaluate the correlation between the AE and test device or operation, and classify according to the following criteria:

(1) Correlation with test device

1) Definitely relevant: The reaction conforms to the known reaction type of the suspected product.

2) Possibly related: The reaction conforms to the known reaction type of the suspected product; The patient's clinical status or other treatment methods may also produce this reaction.

3) Possibly irrelevant: The reaction does not quite conform to the known reaction type of the suspected product; The patient's clinical status or other treatment methods may produce this reaction.

4) Definitely irrelevant: The reaction does not conform to the known reaction type of the suspected product; The patient's clinical status or other treatment methods may produce this reaction, and the disease state may be improved or the reaction may be eliminated by withdrawal of other treatment methods, and present again upon the repeated use of other treatment methods.

5) Unable to judge: The reaction is similar to the known reaction type of the suspected product, and other treatments used at the same time may also cause the same reaction.

(2) Correlation with operation

1) Definitely relevant: The reaction conforms to the known reaction type of the operation.

2) Possibly related: The reaction conforms to the known reaction type of the operation; The patient's clinical status or other treatment methods may also produce this reaction.

3) Possibly irrelevant: The reaction does not quite conform to the known reaction type of the operation; The patient's clinical status or other treatment methods may produce this reaction.

4) Definitely irrelevant: The reaction does not conform to the known reaction type of the operation; The patient's clinical status or other treatment methods may produce this reaction, and the disease state may be improved or the reaction may be eliminated by withdrawal of other treatment methods, and present again upon the repeated use of other treatment methods.

5) Unable to judge: The reaction is similar to the known reaction type of the operation, and other treatments used at the same time may also cause the same reaction.

13.1.4 Possible AEs in this trial and corresponding treatments

13.1.4.1 Common complications and corresponding treatments

(1) Occluder dislocation: Preoperative multi-sectional measurements of ASD size are helpful for selection of indications and occluders. Improper selection of occluder can easily cause dislocation. Through observing the position of the development site and the shape of the left and right discs of the occluder by TTE combined with chest X-ray, it can be judged whether the occluder falls off. If the occluder falls off, it should

be taken out with catcher. If the occluder is large or difficult to take out, the emergency surgery should be performed.

(2) High-grade atrioventricular block: If degree III atrioventricular block occurs during the operation and is still not recovered after long-term suspension of operation, the interventional therapy should be abandoned; Drug treatment should be given in time if degree III atrioventricular block occurs after operation. The device should be removed by surgery and ASD should be repaired if the drug therapy is ineffective;

(3) Cardiac tamponade: Cardiac tamponade can be judged by TTE. Emergent pericardial puncture should be performed for blood drainage and decompression to relieve tamponade, temporarily change the hemodynamics, and contend for rescue time. Meanwhile, saline and blood should be infused to correct hemorrhagic shock. Furthermore, emergency thoracotomy exploration should be prepared. Strict anesthesia management is required and cardiac arrest should be strictly prevented. Sufficient blood should be replenished. Blood accumulated in pericardium cavity should be removed during operation. Normal systolic and diastolic function of heart should be restored. Heart damage should be repaired accurately. Close monitoring of cardiac function and rational application of cardiovascular active drugs are required after operation;

(4) Air embolism: It can be judged by TTE combined with chest X-ray. Oxygen should be inhaled immediately, atropine should be given to patients with slow heart rate, and nitroglycerin should be adopted at the same time to prevent vasospasm;

(5) Residual shunt above medium: It can be judged by TTE. If the diameter of residual shunt is larger than 5 mm and has hemodynamic significance, it is recommended to block the residual shunt again;

(6) Intractable headache or migraine: If the subject complains of headache or migraine symptoms, it can be judged according to headache score or MIDAS migraine score: headache score > 2 can be judged as intractable headache, MIDAS migraine score > 1 can be judged as intractable migraine. Corresponding treatments such as hyperbaric oxygenation should be adopted, aspirin should be taken for at least half a year after operation, and anticoagulation therapy can be combined if necessary. (Appendix 2: headache questionnaire and scoring, Appendix 3: MIDAS migraine questionnaire and scoring);

(7) Cerebral embolism: It can be judged by the clinical manifestations of the subjects with the assistance of brain CT and TTE. The principle of treatment is to improve brain circulation, prevent re-embolism, eliminate brain edema and protect brain function. In acute stage, bed rest should be taken. The respiratory tract should be kept unobstructed and cardiac function should be protected. The nutritional status should be monitored and the balance of water and electrolytes should be kept. Nursing should be strengthened to prevent pneumonia, urinary infection and bedsore. According to the different sources of emboli, symptomatic treatments, including general treatment, surgery, interventional surgery, etc., can be adopted. Relevant surgical guidelines can be referred for operating procedures. Strict anticoagulation during and after operation is the key to prevent embolic events.

13.1.4.2 Expected and unexpected SAEs and corresponding treatments

(1) All-cause death: refers to death of any cause (including cardiac death, non-cardiac death and unexplained death) occurred within the follow-up time. In case of death, the investigator should judge whether it is related to the device and report it to the relevant departments according to the SAE reporting process. The medical and patient commissioner of the sponsor shall be responsible for coordinating the sponsor company and the insurance company to handle the claim settlement procedures;

(2) Intima injury and thromboembolism at puncture site: femoral vein intima injury and thromboembolism may occur due to repeated introduction of interventional materials during operation, excessive operation time, increased blood flow blocking time or rough operation. Thrombolytic therapy is needed and surgery can be conducted to remove thrombus if necessary;

(3) Arteriovenous fistula or pseudoaneurysm: Intraoperative puncture may lead to arteriovenous fistula or pseudoaneurysm. Once it happens, the subject's hospitalization time may be prolonged. Arteriovenous fistula can be treated by surgeries such as fistula repair. Surgical treatment such as ligation of the parent site and aneurysm resection should be performed if the hematoma site of pseudoaneurysm cannot be absorbed by itself;

(4) Other unexpected SAEs.

13.1.4.3 Expected and unexpected AEs and corresponding treatments

(1) Transient arrhythmia: It is usually diagnosed by ECG, which is mostly transient during operation without special treatment;

(2) Fever: It can be judged by clinical examination. The investigators usually need to analyze the cause of fever and treat it symptomatically;

(3) Other unexpected AEs

13.2 Definition of SAE

It refers to death or serious deterioration of health during clinical trial, including

(1) Fatal illness or injury;

(2) Permanent defects in body structure or function;

(3) Requiring hospitalization or prolonged hospitalization;

(4) Medical or surgical intervention is needed to avoid permanent defects in the body structure or function;

(5) Fetal distress, fetal death, congenital abnormality, congenital defect and other events

13.2.1 Treatment of serious adverse events

(1) If serious adverse events occur in the clinical trial, the investigator shall immediately take appropriate treatment measures, and meanwhile provide a written report to the medical device clinical trial management department of the clinical trial institution to which it belongs and notify the sponsor in writing;

(2) The medical device clinical trial management department shall provide a written report within 24 hours to the corresponding ethics committee, the food and drug regulatory authority and the health and family planning department of the province, autonomous region or municipality where the clinical trial institution is located;

(3) In case of deaths, the clinical trial institution and the investigator shall submit all necessary information to the ethics committee and the sponsor;

(4) For SAEs and device deficiencies that may lead to SAEs, the sponsor should report to the drug regulatory agencies and the health and family planning department at the same level within 5 working days after being informed. The sponsor should also notify other clinical trial institutions and investigators participating in the trial, and notify the ethics committees of the clinical trial institutions in time through their medical device clinical trial management departments.

13.3 Device deficiencies

13.3.1 Definition of device deficiency

Device deficiency refers to unreasonable risks of medical devices that may endanger human health and life safety under normal use conditions in the process of the clinical trial, such as label errors, quality problems, malfunctions.

13.3.2 Possible device deficiencies in this trial

(1) Possible device deficiencies include label error, plastic thread damage, ineffective fastening or releasing of locking pieces, displacement of shunt blocking membrane, etc.

(2) Device deficiencies are recorded in the device defect record sheet, and device defects that may lead to serious adverse events will be reported and recorded within 5 working days.

(3) If there are device deficiencies before operation, such as label error, plastic thread damage, ineffective fastening or releasing of locking piece, displacement of shunt blocking membrane, it is necessary to change a new absorbable ASD closure system for operation. In case of device deficiencies such as ineffective fastening or releasing of the locking piece during operation, multi-angle adjustment or pulling can be tried, and if necessary, the device can be reclaimed or taken out with the catcher.

14. Device management

14.1 Investigational device management

Trial institutions should establish strict registration system for the distribution of investigational device, and the sponsor should send the investigational device directly to the clinical trial institutions. The clinical trial institutions and the sponsor should establish perfect device receiving procedures, and the records should include

the handover date, quantity and serial number. Each trial institution should use a special *Record Form for the Use of Medical Devices in Clinical Trials*, and registers the name of the subject, the date of use, and the signature of the device administrator.

14.2 Package of device

Investigational device should be uniformly packaged and numbered, and the packaging bag should be marked with the number, name, production date, expiration date and the words "test".

14.3 Recollection of surplus devices

After the termination of the trial, the sponsor will collect all the investigational devices. The sponsor is responsible for destroying the unused medical devices. At the end of the trial, all relevant materials must be counted.

15. Protocol Deviation and amendment

15.1 Protocol Deviation

Deviation is an intentional or unintentional failure to comply with the requirements of a clinical trial protocol.

15.1.1 Actions to control deviation

Sponsor

(1) Protocol should be described in clear language. The possible protocol deviations should be considered, and the protocol should be designed in a way that minimizes such deviations and ensure that the possible deviations from the protocol can be found and confirmed simply and clearly;

(2) In the investigator meeting and CRA training of the research project, training should be focus on the implementation details of the protocol and the report and supervision of protocol deviation.

Investigator

(1) At the project approval and evaluation stage before the start of the study, read the study protocol carefully and fully discuss the feasibility of the plan in the institution with the sponsor;

(2) The investigators should explain to the subjects the importance of comliance during the process of informed consent;

(3) The investigators should comply with the protocol approved by the ethics committee, and once they realize the protocol deviation, they should immediately record and explain the situation.

15.1.2 Re-training

In order to ensure that the clinical trial is carried out in strict accordance with the clinical protocol approved by

the ethics committee, the investigators need to be retrained for trial protocol if necessary, including but not limited to the following situations:

- The investigators' understanding of the protocol is biased;
- New investigators join in the trial and need to train them;
- Trial protocol or plan is changed;
- It is necessary to remind the investigators of the details of the protocol.

If necessary, investigators can be trained for multiple times.

15.1.3 Report of protocol deviation

(1) If there is a protocol deviation that affects the rights and interests, safety and health of subjects or the scientific nature of clinical trial, including requesting and reporting deviations; The investigators should timely report to the administrative department of medical device clinical trial of the clinical trial institution, and inform the sponsor and report to the ethics committee in time to judge whether the trial can continue;

(2) In order to protect the rights, safety and health of the subjects, if the deviation occurs in an emergency cannot be reported in time, it should be reported in written form as soon as possible in accordance with relevant regulations afterwards;

(3) The revision of clinical trial protocol, informed consent form, and other documents, requesting deviation and resuming the suspended clinical trial during the clinical trial process should obtain written approval from the ethics committee before implementation.

(4) The investigators should strictly follow the clinical trial protocol, and should not deviate from the protocol or substantially change the protocol without the consent of the sponsor and the ethics committee, or without the approval of the NMPA in accordance with the regulations. However, in the case of immediate danger to the subject and other emergency situations requiring immediate elimination, it can also be reported in written form afterwards.

15.2 Protocol amendment

During the trial, if there are major flaws in the clinical trial protocol, such as irrational inclusion/exclusion criteria, indications and evaluation indicators, etc., it should be discussed and revised at the researcher coordination meetings and then reported to the ethics committee for approval or record after unanimous consent.

16. Data access

(1) The authorized CRA has the right to access and verify the source data/files of the subjects, so as to judge whether the investigators conduct the clinical trial according to the requirements of the protocol and whether the source data/files are recorded in the patient's medical records in time. The CRA should confirm that the source data/files are traceable and verifiable. Meanwhile, the data filled in CRF should correspond

to the source data/files;

(2) When any person participating in the clinical trial has doubts about the clinical trial data, the investigators should provide the source data/files in time for the relevant personnel to verify, and earnestly answers the relevant questions;

(3) The source data/files should be properly preserved in accordance with the requirements of relevant laws and regulations. Any destruction can be carried out only after the signature and confirmation of the sponsor, and should meet the requirements of relevant laws and regulations.

17. Finance and insurance

(1) The sponsor of this clinical trial is responsible for providing the medical devices needed for this clinical trial, and providing the fees for the test items required in this clinical trial. The sponsor should bear the cost of treatment and the corresponding economic compensation for the subjects who have suffered injury or death related to clinical trial, except for the damage caused by the fault of medical institutions and their medical staff in the diagnosis and treatment activities;

(2) The specific requirements of finance and insurance are detailed in the relevant agreements;

(3) Medical accidents refer to accidents leading to personal injuries, which is negligently caused by the medical institutions and their medical staff in medical activities due to violation of the medical and health management measures, administrative regulations, trial protocols and guiding principles.

18. Confidentiality

(1) The investigator must keep the study results, protocols and other materials strictly confidential, and shall not release such information without the sponsor's written authorization. If any quotation is needed, written authorization from the sponsor must also be obtained in advance;

(2) All personal information of the subjects is private. Except for the relevant study personnel, only the sponsor of this study project, members of the ethics committee and the relevant personnel of the State/Local Food and Drug Administration can be allowed to access it. The investigator and the sponsor shall keep the subjects' personal information confidential.

19. Publication agreement of trial results

The sponsor and the investigator shall agree on the final study report. The study results can be made public as scientific literature or submitted to the authorities. This clause is designed to protect trade secret materials. All the information about the investigationall device (such as patent application, previously undisclosed production technology and basic scientific data provided by the sponsor to investigators, etc.) is regarded as confidential, and its ownership belongs to the sponsor. The investigators should not use such information for other purposes without the written permission of the sponsor. Before the results of this study are made public or published, the

investigators shall allow the sponsor to review the manuscript and make comments, confirm that no confidential information is disclosed, and supplement relevant information within 30 days. According to the generally accepted principles of scientific research cooperation, the investigators shall discuss the manuscript with relevant personnel of the sponsor and reach an agreement prior to publication.

20. Responsibilities of parties

20.1 Sponsor responsibilities

(1) Select medical institutions according to laws;

(2) Provide Investigator's Brochure to participating institutions;

(3) Jointly design and formulate the clinical study protocol of the medical device with participating institutions, and sign the protocols and contracts of the medical device agreed by both parties;

(4) Provide the investigational devices to participating institutions free of charge;

(5) Train the clinical trial personnel;

(6) Truthfully and timely report the SAE to the medical products administration departments of the provinces, autonomous regions and municipalities responsible for the medical device registration and the safety supervision department of NMPA, and notify others medical institutions participating in the clinical trial.

(7) Before suspending the clinical trial of medical device, the sponsor should notify the medical institutions, EC, the medical products administration departments of the provinces, autonomous regions and municipalities responsible for the medical device registration and NMPA, and explain the reasons;

(8) For damage caused by the investigational device to the subjects, the sponsor should compensate the subjects according to the relevant laws and regulations.

20.2 Responsibilities of institutions and investigators

(1) Should be familiar with the relevant information provided by the sponsor, and familiar with the use of the investigational device;

(2) Jointly design and formulate the clinical trial plan with the sponsor, and sign the clinical trial plan and contract with the sponsor;

(3) Faithfully explain the details of the investigational device to the subjects. The subjects must be given sufficient time to consider whether to participate in the clinical trial before the trial begins.

(4) Record the AE of the investigational device truthfully and analyze the reasons. In case of AE events, they should be truthfully and timely reported to the drug administration of the province, autonomous region or municipality respectively that accepts the application for the medical device registration. The SAE shall be

reported within 24 hours of occurrence;

(5) When AE events occur, investigators should make clinical judgment in time and take measures to protect the interests of subjects; If necessary, the ethics committee has the right to immediately suspend the clinical trial;

(6) If the clinical trial is suspended, institutions and investigators should inform the subject, the sponsor, the ethics committee, the drug regulatory department and the NMPA of the province, autonomous region or municipality that accepts the application for of the medical device registration, and explain the reason;

(7) Submit a clinical trial report and be responsible for the validity and reliability of the report.

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22. Supplementary provisions

Meaning of academic terms involved in this trial protocol:

22.1 Medical device clinical trial institution: refers to the medical institution that undertakes the clinical trial of medical devices as recognized by NMPA and National Health and Family Planning Commission. Unless otherwise specified, "clinical trial institution" in this protocol refers to "medical device clinical trial institution".

22.2 Investigational medical device: refers to the medical device to be registered for verifying or validating their safety and effectiveness in clinical trials.

22.3 Sponsor: refers to the institution or organization that initiates, manages and provides financial support for clinical trials.

22.4 Investigator: refers to the person responsible for implementing clinical trials in clinical trial institutions. If the trial is conducted by a group of people in a clinical trial institution, the investigator refers to the person in charge of the group, which is also called principal investigator.

22.5 Ethics committee: refers to an independent institution set up by clinical trial institutions to examine the scientific and ethical nature of clinical trial items of medical devices.

22.6 Medical device clinical trial management department: refers to the office or department set up in the clinical trial institution to be responsible for the organization, management and quality control of medical device clinical trials.

22.7 Multi-center clinical trial: refers to clinical trial conducted in three or more (including three) clinical trial institutions according to the same clinical trial protocol.

22.8 Subject: refers to an individual who is recruited to accept clinical trial of medical device.

22.9 Informed consent: refers to the process in which the subject confirms to voluntarily participate in the clinical trial after being informed of all aspects of the clinical trial, and the signed and dated informed consent form should be used as the supporting document.

22.10 Informed consent form: refers to the documentary evidence that the subjects express their willingness to participate in clinical trials.

22.11 Monitoring: refers to the activity that the sponsor selects special personnel to evaluate and investigate the clinical trial institutions and investigators, and verify the data in the clinical trial process, record and report it in order to ensure that the clinical trial can follow the protocol, standard operating procedures, *Good Clinical Practice of Medical Devices* and relevant applicable management requirements.

22.12 CRA: Clinical research associate refers to the special personnel selected by the sponsor to monitor the clinical trial items of medical devices.

22.13 Audit: refers to systematic and evaluation of independent inspection of activities and documents related to clinical trials organized by the sponsor to determine whether the implementation of such activities, data recording, analysis and reporting conform to the clinical trial protocol, SOPs, *Good Clinical Practice for Medical Devices* and relevant applicable management requirements.

22.14 Auditor: refers to the person entrusted by the sponsor to check the clinical trial of medical devices.

22.15 Inspection: refers to the activities of the drug regulatory agencies to review, supervise and manage the relevant documents, facilities, records and other aspects of clinical trial.

22.16 Inspector: refers to the personnel selected by the regulatory authorities to inspect the clinical trial of medical devices.

22.17 Deviation: refers to the situation of intentionally or unintentionally failing to comply with the requirements of clinical trial protocol.

22.18 Case report form: refers to the document designed according to the clinical trial protocol to record all the information and data of each subject obtained during the trial.

22.19 Endpoint: refers to the index used to evaluate the hypothesis of clinical trials.

22.20 Source data: refers to the original records of clinical findings, observations and other activities in clinical trials and all information in their approved copies, which can be used for reconstruction and evaluation of clinical trials.

22.21 Source file: refers to printed files, visual files or electronic files containing source data.

22.22 AE: refers to adverse medical events occur during clinical trials, whether related to the investigational device or not.

22.23 SAE: refers to the death or serious aggravation of health during clinical trial, including fatal diseases or injuries, permanent defects in body structure or body function, hospitalization or prolonged hospitalization, and medical or surgical intervention required to avoid permanent defects in body structure or body function, fetal distress, fetal death, congenital abnormality and congenital defect.

22.24 Device defect: refers to unreasonable risk that may endanger human health and life safety under normal use conditions during the clinical trial, such as label error, quality problem, malfunction, etc.

22.25 Standard operating procedure: refers to the standards and detailed written procedures drawn up for effectively implementing and completing each step in clinical trial.

22.26 Clinical data: refers to the safety and performance information obtained from relevant literatures or clinical use of medical devices.

23. List of participating personnel

Clinical trial personnel	Position	Title	Department

Investigator Statement

I agree:

1. Carry out the clinical trial in strict accordance with the Helsinki Declaration, the current Chinese regulations and the requirements of this trial protocol.

2. Record all required data accurately in the CRF, and complete the clinical trial report on time.

3. Only use the device for this clinical trial. The receipt and use of the experimental devices will be completely and accurately recorded during the clinical trial, and records will be kept.

4. Allow clinical research associates, inspectors and regulatory authorities authorized or dispatched by the sponsor to supervise, verify and inspect the clinical trial.

5. Strictly fulfill the clinical trial contract/agreement signed by both parties.

I have read all of the clinical trial protocol, including the above statement, and I agree with all of them.

Sponsor Opinion: Sign: Date:
Investigator Opinion: Approval Sign: Zhiwei Zhang Date: 21 Dec 2019
Clinical trial institution opinion: Approval Sign: National Drug Clinical Trial Institution of Guangdong Provincial People's Hospital Date: 9 Jan 2020

Appendix 1: List of participating institutions and investigators

No.	Institution	Investigator	Title
1	Guangdong Provincial People's Hospital	Zhiwei Zhang	Professor/Director
2	Fuwai Hospital, Chinese Academy of Medical Sciences	Xiangbin Pan	Professor/Director
3	Shanghai Children's Medical Center Affiliated to Shanghai Jiaotong University School of Medicine	Fen Li	Professor/Director
4	Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Sun Chen	Professor/Director
5	Shenzhen Children's Hospital	Cong Liu	Professor/Director
6	Children's Hospital Affiliated to Zhejiang University School of Medicine	Fangqi Gong	Professor/Director
7	Jiangsu Provincial People's Hospital	Xiangqing Kong	Professor/Director
8	Children's Hospital of Chongqing Medical University	Qijian Yi	Professor/Director
9	The First Affiliated Hospital of Guangxi Medical University	Kai Huang	Professor/Director
10	The Second Xiangya Hospital of Central South University	Zhenfei Fang	Professor/Director
11	The Second Affiliated Hospital of Wenzhou Medical University	Rongzhou Wu	Professor/Director
12	Fuwai Central China Cardiovascular Hospital	Taibing Fan	Professor/Director
13	General Hospital of Northern Theater Command	Qiguang Wang	Professor/Director
14	Fujian Medical University Union Hospital	Lianglong Chen	Professor/Director

Appendix 2: Headache questionnaire and evaluation

This questionnaire is used to express how you feel about headache and the negative impact of headache on your life. Please choose one answer from five choices.

1. When you have a headache, how often does severe pain occur?

A. Never B. Seldom C. Sometimes D. Often E. Always

2. Does the headache limit your ability to daily activities, such as housework, work, school, or social activities?

A. Never B. Seldom C. Sometimes D. Often E. Always

3. Do you often wish to lie down when you have a headache?

A. Never B. Seldom C. Sometimes D. Often E. Always

4. In the past 4 weeks, do you often feel tired due to headache and feel powerless in work or daily activities?

A. Never B. Seldom C. Sometimes D. Often E. Always

5. In the past 4 weeks, do you often feel bored and restless due to headache?

A. Never B. Seldom C. Sometimes D. Often E. Always

6. In the past 4 weeks, have you been unable to concentrate on work and daily activities due to headache?

A. Never B. Seldom C. Sometimes D. Often E. Always

Evaluation:

Choose A: 6 scores, choose B: 8 scores, choose C: 10 scores, choose D: 11 scores, choose E: 13 scores.

Add up the corresponding points for all the answers.

Total score range: 36 - 78

Level 1: ≤49, no or minor impact

Level 2: 50-55, moderate impact

Level 3: 56-59, significant impact

Level 4: ≥60, seriously impact

Appendix 3: MIDAS Migraine Questionnaire and score

Five questions were asked to assess the time lost (days) due to migraine over a three-month period. The time loss mainly means paid work, household work, family and social activities. The MIDAS score is obtained by adding all days lost.

1. In the past 3 months, how many days have you been unable to go to work or school due to headache?

_____Days

2. In the past 3 months, how many days have you partially affected your work or study due to headache (efficiency was decreased by more than half)?

_____Days

3. In the past 3 months, how many days have you been unable to do housework due to headache?

_____Days

4. In the past 3 months, how many days have you partially affected your housework due to headache (efficiency was reduced by more than half)?

_____Days

5. In the past 3 months, have you missed visiting friends and relatives, parties, entertainment such as watching TV, playing cards and other similar activities due to headache?

_____Days

Total days:_____Days

Score definition of MIDAS Migraine Disability Assessment Questionnaire

Grading	Degree	Disable Level	Suggestion
0-5	I	Slight or infrequent impact	There is little need for medical intervention. Simple symptomatic treatment can be used with OTC drugs when seizures occur, but the following conditions should be noted: 1. Evaluate the impact of days off due to headache on subjects' life 2. Subjects with infrequent but severe headache need regular treatment 3. Subjects whose headaches are not effectively relieved by painkillers alone need standardized treatment

6-10	II	Mild or frequent impact	Subjects usually have headache for a long time or severe degree, which cannot be completely relieved by analgesic alone and has obvious influence on life. Standardized treatment is needed in the acute phase.
11-20	III	Moderate impact	Headache has serious influence on life. Standardized treatment is needed in the acute phase.
>21	IV	Serious impact	Need preventive treatment.