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

Statistical Analysis Plan

V1.0

Study protocol No.: 42CT（CN）

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Abbreviation or Specialist Term
AE	Adverse Event
ASD	Atrial Septal Defect
BMI	Body mass index
CHD	Congenital Heart Disease
CRF	Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
NRI	Non-responder Imputation
PLLA	Poly-L-lactic Acid
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SOC	System organ class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment emergent adverse event
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography

1. INTRODUCTION

This Statistical Analysis Plan（SAP）is specifically designated for the clinical trial initiated by Lifetech Scientific (Shenzhen) Co., Ltd.: Clinical Trial to Evaluate the Safety and Efficacy of Absnow™ Absorbable ASD Closure System for ASD Patients. This SAP includes the analysis population definition, derived variables, and statistical analysis methods.

2. PRIMARY OBJECTIVE

The primary objective of this clinical trial is to evaluate the safety and efficacy of Absnow™ Absorbable ASD Closure System for ASD patients.

3. STUDY PLAN

3.1. Study Design

This study is designed as a prospective, multicenter, single-arm trial. Through screening, subjects meeting the inclusion and exclusion criteria will be enrolled and undergo implantation of the Absnow™ Absorbable ASD Closure System to assess the safety and efficacy of this study device.

This study plans to enroll 142 subjects from 14 sites in China, and each site will enroll no more than 50% of the total subjects. After undergoing the procedure, follow-up visits will be conducted at nine time points: Before discharge, 30 days, 90 days, 180 days, 360 days, 2 years, 3 years, 4 years, and 5 years post-procedure. An interim analysis of the study will be conducted using the follow-up data obtained within 360 days post-procedure. The results of this interim analysis will be used to support the submission of a marketing authorization application to the National Medical Products Administration (NMPA).

Before the official launch of the nationwide multicenter study, a pilot study with a planned enrollment of 5 subjects will be conducted. Data from these subjects will not be included in the overall efficacy analysis population or the final sample size calculation.

3.2. Study Endpoints

3.2.1. Primary Endpoints

Primary efficacy endpoint: Effective closure rate at 360-day post operation:

Effective closure is defined as no or only a trivial to small residual shunt (based on left-to-

right Doppler flow signals with a diameter <5mm) as assessed by TTE or TEE after device implantation.

Primary safety endpoint: Rate of common complications during 360 days post operation:

Common complications include occluder displacement, high-grade atrioventricular block, cardiac tamponade, air embolism, moderate or larger residual shunt, intractable headache or migraine, and cerebral embolism.

3.2.2. Secondary Endpoints

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

3.2.3. Other Safety Endpoints

- Incidence of device-related Adverse Events (AE);
- Incidence of Serious Adverse Events (SAE)；
- Lab test indicator;
- 12-lead ECG indicator;
- Imaging examination (Chest X-ray and Echocardiography)
- Vital signs indicator.

4. STATISTICAL CONSIDERATION

For continuous variables, the following will be listed: number of valid cases, mean, standard deviation, median, 25th and 75th percentiles, minimum value, and maximum value. The number of decimal places for the 25th and 75th percentiles, minimum, and maximum values will match the records in the database. The mean and median will retain one more decimal place than the raw data recorded in the database, while the standard deviation will retain two more decimal places than the raw data recorded in the database.

For categorical variables, data will be presented in frequency tables (frequencies and percentages). Percentages will be rounded to one decimal place. When the frequency is zero, only the frequency needs to be listed; the percentage may be omitted to distinguish it from non-

zero values. When calculating percentages, the number of subjects in the specified analysis population will serve as the denominator.

All hypothesis tests employ one-sided tests unless otherwise specified, with a statistical significance level of α=0.025. Differences are considered statistically significant when P<0.025. All confidence intervals were calculated at the 95% confidence level. P-values were rounded to three decimal places. If P < 0.001, the value was output as "<0.001". If P > 0.999, the value was output as ">0.999".

All analyses in the safety evaluation are based on observed data, without considering data imputation. For table analyses based on the safety analysis set, all subjects receiving at least one treatment with the study device will be included in the analysis. However, for listing analyses, all subjects with safety evaluations will be included, even if they did not receive any trial treatment.

Unless otherwise specified, baseline data shall be defined as the last valid measurement taken before the implant procedure.

When multiple observation data points exist for the same examination at the same follow-up time point, the observation closest in time to the scheduled visit date will be designated as the primary analysis record for the relevant statistical analysis.

Statistical analysis was performed using SAS 9.4® software. Subject information and safety databases were exported and stored in SAS XPORT format.

4.1. Analysis data set

Screening refers to subjects who signed the informed consent form and participated in the screening process for this study. Enrollment indicates subjects who met the inclusion/exclusion criteria following assessment.

4.1.1. Full Analysis Set (FAS)

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 a study device in the body.

If the implantation is abandoned due to other clinical reasons and there is no investigational device in the body, such subject 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.

4.1.2. Safety Set (SS)

Safety Set will include all subjects who have been treated with the device at least once and have safety evaluation data. SS will be the main data set for other safety analysis excepting the primary safety endpoints.

4.1.3. Per-Protocol Set (PPS)

Per-Protocol Set refers to subjects who have no serious protocol deviation 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. Subjects who did not complete the full visit schedule for any reason should theoretically be excluded from the PPS. However, this exclusion does not apply if existing results already determine whether the subject successfully underwent treatment for atrial septal defect. treated can be judged according to the existing results. PPS will be the secondary data set for efficacy evaluation.

4.2. Missing Data and Unreasonable Data

For primary efficacy and safety endpoints, if a subject withdraws from the trial prior to the 360-day follow-up or has missing data for the primary endpoint at the 360-day follow-up, Non-responder Imputation (NRI) will be applied to impute the missing values. For the primary efficacy endpoint of 360-day effective closure rate, if a subject's 360-day follow-up data is missing, that subject will be imputed as “ineffective.” For the primary safety endpoint of common complication

incidence within 360 days post-operation, if a subject's safety follow-up data within 360 days is incomplete due to lost to follow-up or other reasons, that subject will be imputed as having "experienced a common complication."

5. ENDPOINTS ANALYSIS

5.1. Primary Endpoints Analysis

For primary efficacy endpoints and safety endpoints, statistical inference will be based on the FAS and PPS. The FAS will serve as the primary dataset for primary endpoint analyses, while the PPS will be the secondary dataset.

5.1.1. Primary efficacy endpoints

Primary efficacy endpoint is effective closure rate at 360-day post operation. Effective closure is defined as no or only a trivial to small residual shunt (based on left-to-right Doppler flow signals with a diameter <5mm) as assessed by TTE or TEE after device implantation.

For the primary efficacy endpoint evaluation, the following hypotheses are tested:

Null hypothesis $H_0: \pi_1 \leq \pi_0$. That is, the Absnow Absorbable Atrial Septal Defect Occluder System fails to meet the design requirement for the 360-day post-operation effective closure rate.

Alternative hypothesis $H_1: \pi_1 > \pi_0$. That is, the Absnow Absorbable Atrial Septal Defect Occluder System meets the design requirement for the 360-day post-operation effective closure rate.

π_1 refers to the expected 360-day post-operation effective closure rate， π_0 refers to the Objective Performance Criteria (OPC) value of 360-day post-operation effective closure rate

Statistical inference will be performed using the exact method to estimate the 95% confidence interval (CI) for the effective closure rate at 360 days post-operation, as well as the P-value for comparison with the predefined performance goal of 94%. If the lower limit of the two-sided 95% CI for the effective closure rate at 360 days exceeds 94%, the null hypothesis will be rejected, and it will be concluded that the Absnow Absorbable Atrial Septal Defect Occluder System meets the

design requirement for the 360-day post-operation effective closure rate. Otherwise, it cannot be concluded that the 360-day effective closure rate meets the predefined performance requirement.

If a subject has missing valid data at 360 days, the subject will be imputed as "ineffective" using the Non-responder Imputation (NRI) method. For analyses based on the PPS, missing data will not be imputed.

5.1.2. Primary safety endpoints

Primary safety endpoint is defined as the rate of common complications during 360 days po st operation. For the primary safety endpoint evaluation, the following hypotheses are tested:

Null hypothesis H_0: $\pi_1 \leq \pi_0$. That is, the Absnow Absorbable Atrial Septal Defect Occluder System fails to meet the design requirement for the 360-day common complications rate.

Alternative hypothesis H_1: $\pi_1 > \pi_0$. That is, the Absnow Absorbable Atrial Septal Defect Occluder System meets the design requirement for the 360-day post-operation common complications rate.

π_1 refers to the expected 360-day post-operation common complications rate，π_0 refers to the Objective Performance Criteria (OPC) value of 360-day post-operation common complications rate.

Statistical inference will be performed using the exact method to estimate the 95% confidence interval (CI) for the common complications rate at 360 days post-operation, as well as the P-value for comparison with the predefined performance goal of 6%. If the upper limit of the two-sided 95% CI for the common complications rate at 360 days is less than 6%, the null hypothesis will be rejected, and it will be concluded that the Absnow Absorbable Atrial Septal Defect Occluder System meets the design requirement for the 360-day post-operation common complications rate. Otherwise, it cannot be concluded that the 360-day common complications rate meets the predefined performance requirement.

If a subject has missing valid data at 360 days, the subject will be imputed as "common complications occurred" using the Non-responder Imputation (NRI) method. For analyses based on the PPS, missing data will not be imputed.

The above two clinical endpoints are designated as primary endpoints for analysis in this study. A conclusion that the Absnow™ Bioresorbable Atrial Septal Defect Occlusion System meets the requirements for clinical application will be made only if both primary endpoints achieve the predefined performance criteria. Therefore, no adjustment to the significance level (α) is required.

5.2. Secondary Endpoints Analysis

Secondary endpoint is defined as immediate operation success rate, which means that left and right disks are effectively fixed on the left and right sides of the atrial septum, respectively, and smoothly released without displacement or migration, and the delivery system is successfully withdrawn.

Secondary endpoints will be summarized descriptively using frequencies and percentages, a nd no formal statistical inference will be performed. However, the 95% confidence interval for th e immediate operation success rate will be calculated using the exact method.

6. SAFETY ANALYSIS

Safety evaluation endpoints include adverse events, laboratory test results, electrocardiogram (ECG) results, imaging assessments (chest X-ray and echocardiography), and vital signs. All safety endpoints will be analyzed descriptively based on the SS.

6.1. Adverse Events

Adverse events that may occur in this study include: (1) common complications; (2) expected or unexpected serious adverse events (SAEs); and (3) expected or unexpected adverse events (AEs). All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0.

All treatment-emergent adverse events (TEAEs) occurring during the study period will be

included in the analysis, including events occurring intraoperatively and postoperatively. The following categories of adverse events will be summarized by the number and percentage of subjects: TEAEs, serious adverse events (SAEs), device-related adverse events, device-related serious adverse events, procedure-related adverse events, procedure-related serious adverse events, adverse events leading to study discontinuation, and adverse events resulting in death.

6.1.1. Treatment-emergent Adverse Events

All TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), and the incidence will be presented accordingly. At each level of summarization, if a subject experiences one or more adverse events within a given category, the subject will be counted only once and will not be counted repeatedly. All percentages will be calculated using the total number of subjects in the SS as the denominator.

If the relationship of an adverse event to the investigational device or the procedure is unclear, it will be classified as related for analysis purposes. In the categorization of relationship to the investigational device or procedure, events assessed as possibly related, probably related, or definitely related will be grouped as related, whereas events assessed as not related or unlikely related will be grouped as unrelated.