Safety and Efficacy of Endoscopic Cardial Constriction Ligation （ECCL） With a Novel Disposable Endoscope: A Multicenter Randomized Controlled Trial

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I. Study Background

Currently, traditional endoscopes are reusable, requiring cleaning and disinfection after each use before they can be reused. However, the inability to achieve complete sterilization with traditional endoscopes has garnered increasing attention [1,2]. In contrast, disposable endoscopes eliminate the risk of cross-infection, bypass the cumbersome cleaning and disinfection processes, and reduce the incidence of surgical instrument-related infections. Furthermore, disposable endoscopes are comparable to standard endoscopes in terms of functionality and operability [3].

Gastroesophageal reflux disease (GERD) can be classified based on endoscopic findings into non-erosive reflux disease (NERD), reflux esophagitis (RE), and Barrett's esophagus (BE). Typical symptoms include heartburn and regurgitation, while atypical symptoms encompass chest pain, epigastric pain, abdominal bloating, belching, and extraesophageal symptoms [4]. Epidemiological surveys in China indicate a prevalence of heartburn occurring at least once weekly ranging from 1.9% to 7.0% [5,6]. Chronic, recurrent GERD significantly impairs patients' quality of life and may increase the risk of Barrett's esophagus, esophageal mucosal dysplasia, and esophageal adenocarcinoma. The pathogenesis and progression of GERD involve multiple factors, including increased esophageal acid exposure, lower esophageal sphincter (LES) relaxation, low esophagogastric junction (EGJ) pressure, impaired esophageal clearance, hiatal hernia, and damage to the mucosal barrier by cytokines (e.g., IL-6, IL-8, platelet-activating factor PAF) and heightened reflux sensitivity [7,8].

The first-line treatment for GERD currently involves lifestyle modifications and oral acid-suppressive medications, such as proton pump inhibitors (PPIs) [9] and potassium-competitive acid blockers (P-CABs) [10]. However, some patients with refractory GERD require long-term acid-suppressive therapy, and studies suggest that

prolonged PPI use may increase the risk of Clostridioides difficile infection, community-acquired pneumonia, gastric cancer, and chronic kidney disease [11,12], while short-term P-CAB use may lead to hypergastrinemia [13]. According to the 2020 Chinese GERD Expert Consensus [14], for patients with refractory GERD who fail medical therapy, endoscopic or surgical treatment may be considered after thorough evaluation to rule out other causes and confirm evidence of reflux, with careful consideration of risks and benefits.

Endoscopic cardia constriction ligation (ECCL), first performed by Professor Linghu Enqiang in 2013 [15], operates on principles similar to esophageal and gastric variceal ligation. Specifically, under direct endoscopic visualization, the mucosa and partial muscle layer above the dentate line are ligated to form folds. Post-ligation, the local mucosa undergoes ischemic necrosis and heals to form scar tissue, reducing the cardia diameter, increasing LES pressure, and alleviating reflux symptoms [16,17]. This method is characterized by simple operation and minimal invasiveness, making it safer than traditional surgical or laparoscopic procedures. Related complications, such as bleeding after ligation band detachment and retrosternal pain, have a low incidence and rapid recovery, with no severe adverse events reported to date. However, the long-term efficacy of ECCL requires further validation through prospective, large-scale studies.

In recent years, endoscopic treatments for refractory GERD have continued to evolve, but there are currently no studies on the efficacy and adverse event rates of ECCL performed using disposable endoscopes. Therefore, this study aims to conduct a randomized controlled trial to compare the effectiveness, safety, flexibility, and imaging clarity of ECCL guided by disposable versus traditional endoscopes in a large sample. The ultimate goal is to optimize treatment strategies, provide scientific evidence for personalized GERD treatment, and inform the development of future GERD treatment guidelines.

II. Study Objectives

1. **Primary Objective**: To compare the efficacy of endoscopic cardia constriction ligation (ECCL) using disposable endoscopes versus traditional endoscopes in the treatment of refractory gastroesophageal reflux disease (GERD).

2. **Secondary Objectives**:

① To evaluate the observation clarity, flexibility, and compatibility of disposable endoscopes with surgical consumables.

② To assess the incidence of device failures and complications related to disposable endoscope-guided ECCL, such as mucosal injury, bleeding, and perforation.

III. Study Endpoints

1. **Primary Endpoint**: Comparison of the effectiveness of ECCL using disposable versus traditional endoscopes in alleviating GERD-related symptoms such as acid regurgitation and heartburn.

Evaluation Method:

- **Pre-procedure**: Patients undergo GERD-Q scoring and endoscopic examination to establish baseline symptoms and endoscopic findings.
- **3 months post-procedure**: Patients are assessed with GERD-Q scoring and queried about GERD-related symptoms and complications.
- **6 months post-procedure**: Follow-up with repeat GERD-Q scoring to compare changes in GERD-Q scores from baseline to post-procedure.

2. **Secondary Endpoints**:

① **Clinical Feasibility of ECCL with Disposable Endoscopes**

Evaluation Method:

○ Feasibility is defined as the ability to successfully retroflex the endoscope behind the cardia, clearly visualize the dentate line, and perform ECCL with the ligation device securely mounted on the endoscope, effectively suctioning the gastric mucosa and smoothly releasing the ligation band. All abnormal findings in the endoscopic report must be photographically documented.

○ A procedure is deemed “feasible” if the entire endoscopic examination and treatment are completed without interruption due to endoscope-related issues. It is deemed “infeasible” if the procedure is terminated due to endoscope malfunctions.

○ Clinical feasibility rate = (Number of successfully completed cases ÷ Total number of participants) × 100%.

② **Effectiveness and Safety of ECCL with Disposable Endoscopes**

○ Record the clarity of endoscopic images, flexibility, and compatibility of required consumables with the endoscope during the procedure.

○ Document any endoscope-related mucosal injury, gastrointestinal perforation, or significant bleeding during the procedure or within 1 hour post-procedure, as well as any surgery-related adverse events (e.g., pain, bleeding, infection) post-procedure.

③ **Device Failure/Defect Rate**

○ Observe and record any device malfunctions during the procedure, such as image interruption, water delivery blockage, or leakage.

3. **Safety Endpoints**:

Primary Safety Endpoints:

① Document any endoscope-related mucosal injury, gastrointestinal perforation, or significant bleeding during the procedure or within 1 hour post-procedure, as well as any surgery-related adverse events (e.g., pain, bleeding, infection) and equipment failures (e.g., image interruption, water flow blockage, or leakage).

Secondary Safety Endpoint:

③ **Procedural Stability**: Assess the stability of participants' blood pressure and heart rate during the procedure, record the number of cases with stable parameters, and calculate the stability rate.

III. Study Design, Methods, and Procedures

1. Study Design

This clinical study is a randomized (1:1), multicenter, parallel-controlled clinical trial. A total of 46 patients will be recruited. Participating centers include Shenzhen Hospital of Southern Medical University, the 964th Hospital of the Joint Logistics Support Force, and the Army Medical Center. The trial employs a multicenter competitive enrollment approach, with each center recruiting participants based on available patient resources and enrollment pace until the total recruitment target is met. All enrolled patients will be randomized using a computer-generated random number table, managed by an independent statistician who ensures allocation concealment. After signing the informed consent form, patients meeting the inclusion/exclusion criteria will be randomly assigned in a 1:1 ratio to either the experimental group (undergoing ECCL with disposable endoscopes) or the control group (undergoing ECCL with traditional endoscopes).

- **Experimental Group**: Participants randomized to the experimental group will undergo ECCL using disposable endoscopes. The procedure involves sequentially suctioning and ligating one band each on the lesser curvature, posterior wall, and greater curvature of the cardia, capturing the

mucosal and muscular layers. A hemostatic clip will be used to secure the base of the ligated tissue on the greater curvature. Six hours post-procedure, patients may consume lukewarm liquid or semi-liquid diets and continue acid-suppressive therapy for two weeks.

- **Control Group**: Participants randomized to the control group will undergo ECCL using traditional endoscopes, following the same procedure: sequentially suctioning and ligating one band each on the lesser curvature, posterior wall, and greater curvature of the cardia, capturing the mucosal and muscular layers, with a hemostatic clip securing the base of the ligated tissue on the greater curvature. Six hours post-procedure, patients may consume lukewarm liquid or semi-liquid diets and continue acid-suppressive therapy for two weeks.

Each participant will be followed up via telephone and outpatient visits at 3 months and 6 months post-procedure.

2. **Study Methods**

(1) **Randomization**

In this study, patients meeting the inclusion/exclusion criteria will be randomly assigned in a 1:1 ratio to the experimental or control group. A computer-generated random number table will be used, managed by an independent statistician who ensures allocation concealment.

(2) **Blinding/Unblinding**

This study will be conducted in an open-label manner. Imaging evaluations and data analysis will be performed by medical professionals independent of the study to ensure objectivity.

3. Study Procedures

Trial Flowchart

Item	Screening Period	Procedure Day	Follow-up Period	Follow-up Period
TIME	-3 to 0 Days	During Procedure	3 Months Post-Procedure	6 Months Post-Procedure)
Informed Consent	X			
Demographics	X			
Inclusion/Exclusion Criteria	X			
Laboratory Tests	X			
Electrocardiogram	X			
Endoscopy	X			
Blood Pressure, Heart Rate	X	X		
GERD-Q Score	X		X	X
Adverse Events		X	X	X
Medication Use	X			

Remarks <

- *Laboratory test results from within 7 days prior to signing the informed consent form are acceptable.*
- *Endoscopy results from within 6 months prior to signing the informed consent form are acceptable.*

IV. Study Population

Patients diagnosed with refractory gastroesophageal reflux disease (GERD) in accordance with the 2023 Chinese Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease.

1. Inclusion Criteria

(1) Age 18–80 years;

(2) Disease duration ≥6 months, with typical symptoms such as acid regurgitation and heartburn, and a confirmed diagnosis of GERD;

(3) GERD patients whose symptoms are not relieved after 8 weeks of continuous double-dose acid-suppressive therapy;

(4) Willing to participate in the study and have signed the informed consent form.

2. Exclusion Criteria

(1) Patients with precancerous lesions such as early esophageal cancer or Barrett's esophagus >3 cm, or advanced upper gastrointestinal cancer identified on endoscopy;

(2) Patients with hiatal hernia ≥2 cm, severe reflux esophagitis (LA-C or LA-D grade), esophageal or gastric varices, esophageal ulcer or stenosis, or a history of esophageal or gastric surgery;

(3) Patients with esophageal motility disorders such as achalasia or diffuse esophageal spasm, rheumatic diseases such as systemic sclerosis or Sjögren's syndrome, or eosinophilic esophagitis;

(4) Patients with a history of endoscopic or surgical anti-reflux procedures;

(5) Patients with coagulation disorders, severe cardiopulmonary diseases, or inability to tolerate anesthesia, endoscopy, or treatment;

(6) Women in the puerperium.

3. Lifestyle Considerations

1. **Smoking**: Patients are advised to reduce or quit smoking to prevent exacerbation of LES relaxation and reflux.

2. **Alcohol Consumption**: Avoid strong liquors and high-alcohol-content beverages to reduce gastric acid secretion.

3. **Exercise**: Avoid vigorous exercise post-procedure; low-intensity activities such as walking or yoga are permitted.

4. **Diet**: Avoid high-fat, spicy foods, and carbonated beverages; consume lukewarm liquid or semi-liquid diets for 2 weeks post-procedure.

5. **Prohibited Medications**: Avoid NSAIDs, anticholinergic drugs, and prokinetic agents; if their use is necessary, patients must report to the study team for evaluation.

6. **Additional Treatments or Surgeries**: If participants require other GERD-related treatments or surgeries, they must notify the study team and may be withdrawn from the trial.

4. **Screening Failure**

Definition: Screening failure refers to participants who, during the initial screening process, fail to meet the inclusion criteria or meet any exclusion criteria, thus being ineligible for randomization.

Management Measures:

1. **Record Reasons for Screening Failure**: Document the specific reasons for ineligibility, such as symptoms not meeting GERD diagnostic criteria or presence of diseases listed in the exclusion criteria.

2. **Inform Participants**: Explain the screening results to participants who fail screening and provide appropriate alternative

treatment recommendations or information about other potential studies.

3. **Data Management**: Data from participants who fail screening will not be included in the final study analysis but may be used to optimize future screening criteria or improve study design.

4. **Follow-up**: For some participants who fail screening, if their symptoms change or they meet inclusion criteria after treatment, they may be reassessed for potential inclusion in the study.

5. Recruitment and Retention Strategies

This study will be conducted at Shenzhen Hospital of Southern Medical University, the 964th Hospital of the Joint Logistics Support Force, and the Army Medical Center. A total of 46 GERD patients meeting the inclusion criteria will be recruited through outpatient screening, inpatient referrals, social media announcements, and patient education seminars, and randomly assigned in a 1:1 ratio to the experimental and control groups. To enhance participant compliance and retention, the study team will maintain contact via telephone, email, and WeChat, providing reminders for post-procedure follow-ups and offering free follow-up visits and GERD-related health consultations. For patients with slow recovery post-procedure, the study team will provide additional health guidance and psychological support. As this study involves GERD treatment, to ensure participant safety, minors and pregnant women will not be included. All participants must sign an informed consent form and be fully informed of the study's objectives, methods, and potential risks. These measures aim to ensure the smooth conduct of the study while safeguarding participants' rights and safety.

6. Evaluation Metrics

(1) **Efficacy Evaluation**:

Primary Endpoint:

① Whether GERD-related symptoms such as acid regurgitation and heartburn are significantly alleviated post-procedure, quantified by changes in GERD-Q scores, Los Angeles (LA) classification, and Hill classification from baseline to post-procedure, and whether these changes are statistically significant.

Secondary Endpoint:

② Feasibility assessment of ECCL. Evaluation parameters include:

- **Image Clarity**:

(A) Good brightness, contrast, and clarity: Able to accurately identify the dentate line of the cardia.

(B) Poor brightness, contrast, or clarity: Unable to identify the dentate line of the cardia.

- **Endoscope Flexibility**:

(A) Endoscope can be smoothly retroflexed.

(B) Endoscope cannot be smoothly retroflexed.

- **Compatibility of Consumables with Endoscope**:

(A) Endoscope is compatible with ligation equipment, allowing smooth operation.

(B) Endoscope is incompatible with ligation equipment, preventing operation.

Assessment Criteria: If all parameters are rated "A," the feasibility of ECCL is deemed "qualified." If any parameter is rated "B," it is deemed "unqualified."

Feasibility Rate Calculation: (Number of "qualified" cases / Total number of patients per group) × 100.

(2) **Safety Evaluation**:

Primary Endpoint:

① Document any endoscope-related mucosal injury, gastrointestinal perforation, or significant bleeding during the procedure or within 1 hour post-procedure, as well as any surgery-related adverse events (e.g., pain, bleeding, infection) and equipment failures (e.g., image interruption, water flow blockage, or leakage).

Secondary Endpoint:

③ **Procedural Stability**: Assess the stability of participants' blood pressure and heart rate during the procedure, record the number of cases with stable parameters, and calculate the stability rate.

V. Study Interventions

1. Intervention Details

This study employs disposable and traditional endoscopes to perform endoscopic cardia constriction ligation (ECCL) to evaluate their safety and efficacy. The experimental group undergoes ECCL using disposable endoscopes, while the control group uses traditional endoscopes, both following a standardized procedure. This includes sequential suction and ligation of one band each on the lesser curvature, posterior wall, and greater curvature of the cardia, capturing the mucosal and muscular layers, with a hemostatic clip securing the base of the ligated tissue on the greater curvature. All participants receive post-procedure acid-suppressive therapy with oral proton pump inhibitors (PPIs) or potassium-competitive acid blockers (P-CABs) and begin consuming lukewarm liquid or semi-liquid diets 6 hours post-procedure. Follow-ups at 3 and 6 months post-procedure assess GERD-Q scores, symptom relief, and complication rates, conducted via telephone, WeChat, or outpatient visits to ensure data completeness and participant compliance.

2. Preparation/Handling/Storage/Responsibilities

This study involves disposable gastrointestinal endoscopes as investigational medical devices, requiring strict management of storage, transportation, and

distribution. The storage conditions for these devices are 5°C–30°C with relative humidity ≤93%, and temperature and humidity records must be maintained during hospital storage to ensure a suitable environment. Device transportation is conducted via courier, managed by the study team, with conditions set at -40°C to 55°C and relative humidity ≤93%. Upon arrival at the hospital, handover procedures must be completed, and devices should be promptly stored.

For device allocation, the experimental and control groups use disposable and traditional endoscopes, respectively, for ECCL. All device assignments are determined through a randomized design with allocation concealment managed by an independent statistician to ensure scientific rigor and impartiality. During the procedure, participants' vital signs, procedural success, device compatibility, and any device-related adverse events must be meticulously recorded and included in the study analysis.

Additionally, the study team must ensure the safe use of devices and provide standardized training to all medical staff to ensure consistency in clinical operations. Any equipment malfunctions or abnormalities during use must be immediately documented and reported to the study team to ensure the smooth conduct of the study.

3. **Concomitant Treatments**

During the study, participants may use acid-suppressive drugs (PPIs or P-CABs), analgesics (acetaminophen), prokinetic agents (mosapride or domperidone), and antibiotics (cephalosporins or quinolones) under medical guidance to optimize post-procedure recovery and ensure scientific validity. Probiotics may be supplemented to maintain gut health, dietary adjustments made to avoid gastric acid stimulation, and psychological interventions applied to alleviate post-procedure anxiety. All concomitant treatments must be documented to ensure data comparability and objectivity.

4. **Emergency Rescue**

In case of emergencies requiring rescue, medical staff may employ targeted medications and treatments, including norepinephrine, ephedrine, or dopamine to elevate blood pressure; desmopressin, thrombin, or blood transfusion to control severe bleeding; endoscopic titanium clips to close small perforations or surgical intervention for larger perforations; naloxone, endotracheal intubation, or mechanical ventilation for respiratory depression or asphyxia; and aspirin, nitroglycerin, or necessary cardiac interventions for myocardial infarction. During rescue, intravenous access must be established, and vital signs monitored in real-time using a multifunctional electronic monitor. Cardiopulmonary resuscitation (CPR) should be performed if necessary, with the emergency team intervening and transferring the patient to the ICU for further treatment. All rescue procedures must be thoroughly documented, including rescue timing, changes in condition, drug dosages, patient responses, monitoring data, surgical interventions, and imaging results, to ensure data completeness and traceability.

VI. Study Intervention Suspension/Participant Termination and Withdrawal

1. **Study Intervention Suspension**

The study may be temporarily suspended under the following circumstances: if serious safety issues arise, such as gastrointestinal perforation, significant bleeding, or severe infection, with an adverse event rate exceeding the preset threshold, or if significant flaws in the clinical trial protocol are identified, rendering it difficult to evaluate the safety and efficacy of the investigational device. Additionally, suspension may occur if regulatory authorities determine that participant rights cannot be guaranteed or if adjustments to the study design are required.

The duration of suspension will depend on the specific circumstances, ranging

from a short-term pause (e.g., 1–2 weeks) for adjustments to permanent termination. During suspension, data collection from enrolled participants will continue, including symptom relief, adverse event rates, and other relevant metrics, to assess the impact of suspension on data integrity.

Resumption of the study requires resolution of critical issues affecting safety or scientific validity, such as optimizing device use, refining procedural protocols, or improving follow-up plans. Resumption must be approved by the ethics committee and regulatory authorities.

During suspension, follow-up of participants will continue as per the original schedule, with symptom assessments and safety monitoring conducted via telephone, WeChat, or outpatient visits. If participants experience adverse reactions or medical needs, the study team will provide medical guidance or recommend appropriate treatment to ensure participant safety.

2. **Participant Termination/Withdrawal from the Study**

Criteria for Study Termination (the study will be terminated if any of the following apply):

1. Serious safety issues occur during the trial;
2. Significant errors are identified in the clinical trial protocol;
3. The study sponsor requests termination of the trial;
4. The ethics committee requests termination of the trial;
5. The device regulatory authority requests termination of the trial.

Participants who withdraw from the study for any reason must have the reason documented, including but not limited to:

1. Withdrawal of informed consent by the participant;
2. Termination of the study by the sponsor;

3. Severe adverse events preventing the participant from continuing in the trial;

4. Significant protocol violations/deviations;

5. Pregnancy;

6. Poor compliance;

7. Loss to follow-up;

8. The investigator and/or sponsor determines that the participant's medical condition may jeopardize their safety or that continued participation could harm their health.

3. **Loss to Follow-Up**

To minimize loss to follow-up and reduce the impact of missing data, the study team will emphasize the importance of follow-up to participants at the outset, provide clear scheduling, and use multiple communication methods (telephone, WeChat, email) to regularly remind participants of follow-up visits. Participants will be required to provide at least two alternative contacts to maintain communication in case of disconnection, ensuring data completeness. Additionally, the study team will offer remote follow-up options, such as online video or telephone interviews, and flexibly adjust follow-up schedules to reduce loss due to distance or time constraints. For occasional missing data, supplementation may be achieved by reviewing past medical records, interviewing participants, or consulting family members. In statistical analyses, missing data will be addressed using intention-to-treat (ITT) analysis or imputation methods to minimize the impact of loss to follow-up on study results.

VII. Detailed Study Procedures

1. All participants must sign an informed consent form prior to screening, and those who successfully pass the screening may proceed to enroll in the study.

2. Participants are treated according to the protocol, with the experimental group undergoing endoscopic cardia constriction ligation (ECCL) using disposable endoscopes and the control group undergoing ECCL using traditional endoscopes.

3. During the procedure, both the experimental and control groups are evaluated and documented for vital signs, procedural success (clinical feasibility of ECCL), endoscopist's operational experience, and occurrence of device-related adverse events.

4. At 3 and 6 months post-procedure, the efficacy and incidence of complications are evaluated and recorded.

1. Screening Period

All participants must complete the screening period assessments before enrollment, adhering to the inclusion and exclusion criteria.

(1) Sign the informed consent form.

(2) Record demographic data: date of birth, sex, and initials.

(3) Collect medical history and perform a physical examination (including vital signs, anal inspection, and digital rectal examination).

(4) Conduct laboratory tests, including complete blood count, coagulation profile (four items), and infectious disease panel (eight items).

(5) Pre-procedure assessments: electrocardiogram, Los Angeles (LA) classification for reflux esophagitis, and Hill classification for hiatal hernia via endoscopy.

2. Treatment Period

Treatment modalities are determined based on pre-procedure randomization.

- **Experimental Group**: Participants undergo ECCL using disposable

endoscopes. The procedure involves sequentially suctioning and ligating one band each on the lesser curvature, posterior wall, and greater curvature of the cardia, capturing the mucosal and muscular layers, with a hemostatic clip securing the base of the ligated tissue on the greater curvature. Six hours post-procedure, participants may consume lukewarm liquid or semi-liquid diets and continue acid-suppressive therapy for two weeks. Vital signs and any surgery-related serious adverse events are recorded during the procedure for statistical analysis.

- **Control Group**: Participants undergo ECCL using traditional endoscopes, following the same procedure: sequentially suctioning and ligating one band each on the lesser curvature, posterior wall, and greater curvature of the cardia, capturing the mucosal and muscular layers, with a hemostatic clip securing the base of the ligated tissue on the greater curvature. Six hours post-procedure, participants may consume lukewarm liquid or semi-liquid diets and continue acid-suppressive therapy for two weeks. Vital signs and any surgery-related serious adverse events are recorded during the procedure for statistical analysis.

3. Follow-up Period

All participants are followed up until 6 months post-procedure.

- At 3 months post-procedure, participants undergo GERD-Q scoring and are queried about GERD-related symptoms and complications via telephone or WeChat.

- At 6 months post-procedure, participants continue to undergo GERD-Q scoring and are queried about GERD-related symptoms and complications via telephone or WeChat.

- Participants experiencing symptoms such as bleeding, fever, or chest pain during the follow-up period must return to the hospital within 24 hours

for blood tests, chest CT, or endoscopic examination to determine the cause of complications.

VIII. Observation, Recording, and Management of Adverse Events

1. Definition of Adverse Events (AE)

An adverse event (AE) refers to any unfavorable medical occurrence in a patient or participant following the administration of a study drug, regardless of whether a causal relationship with the treatment is established. Thus, an AE can include any unfavorable signs (including abnormal laboratory findings), symptoms, or diseases temporally associated with the use of the study drug, whether or not they are considered related to the study drug. AEs encompass both serious adverse events (SAEs) and non-serious adverse events.

2. Definition of Serious Adverse Events (SAE)

An SAE is defined as any medical occurrence during a clinical trial that results in hospitalization or prolongation of hospitalization, disability, impaired work capacity, life-threatening conditions, death, or congenital anomalies. SAEs include the following medical events:

(1) Events leading to death;

(2) Life-threatening events (defined as events posing an immediate risk of death at the time of occurrence);

(3) Events requiring hospitalization or prolongation of hospitalization;

(4) Events leading to permanent or severe disability, functional impairment, or loss of work capacity;

(5) Congenital anomalies or birth defects;

(6) Other significant medical events (defined as events that jeopardize the participant or require intervention to prevent any of the above outcomes).

3. Recording, Collection, Reporting, and Management of Adverse Events

(1) **Collection, Reporting, and Management of AEs**

All AEs related to the study protocol procedures, occurring from the time of signing the informed consent form until the initiation of the study drug, must be recorded in the electronic Case Report Form (eCRF).

AE records should include: a description of the AE and all related symptoms, onset time, severity, duration, relationship to the study drug, measures taken, and final outcome. AEs must be documented using medical terminology, and if a participant's symptoms and signs can be attributed to a single underlying cause, a diagnosis should be recorded whenever possible. Apart from disease progression-related metrics, all clinical events and clinically significant laboratory abnormalities should be managed in reference to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-related adverse reactions will be recorded by the investigator.

(2) **Collection and Reporting of SAEs**

All SAEs occurring from the time of signing the informed consent form until 4 weeks after completion of the study drug administration, regardless of cause or relationship to the study drug, must be reported using the SAE report form. In the event of an SAE, the investigator must immediately implement appropriate treatment measures to ensure participant safety and report the SAE within 24 hours to the drug registration applicant, the National Medical Products Administration, the Provincial Food and Drug Administration, the ethics committee of the respective clinical trial center, and the Medical Administration Department of the Health Commission. The lead institution's ethics committee must also be promptly notified. The initial report should include, to the extent possible, the following details: source of the report, study drug name, SAE name, onset time, severity, duration, relationship to the study drug, measures taken, and outcome.

(3) **Pregnancy**

Women of childbearing potential must use effective contraception methods during the

study period, minimizing the risk of contraceptive failure. Before enrolling women of childbearing potential, the investigator must inform them of the importance of avoiding pregnancy during the study and the potential risks of unintended pregnancy. Participants must sign the informed consent form to confirm that these issues have been discussed and fully understood.

Pregnancy Testing Requirements: All women of childbearing potential must have negative blood pregnancy test results during the screening period and at baseline/day -1. Investigators must also inform all women of childbearing potential to immediately report any suspected pregnancy (e.g., amenorrhea or delayed menstruation) to the study team during the trial.

Pregnancy Reporting: If pregnancy or suspected pregnancy is identified during the administration of the study drug, the study drug must be discontinued. If pregnancy or suspected pregnancy is identified within 3 months after the last dose of the study drug, it must be documented and reported accordingly.

(4) **Severity Assessment of AEs**

Investigators will assess the severity of AEs based on the five-level criteria outlined in NCI CTCAE version 5.0:

- **Grade 1**: Mild; asymptomatic or mild signs; clinical or diagnostic observations only, no medical intervention required.
- **Grade 2**: Moderate; limited age-appropriate instrumental activities of daily living (e.g., cooking, shopping, phone use).
- **Grade 3**: Severe or medically significant but not immediately life-threatening; results in hospitalization or prolongation of hospitalization; disabling; limits self-care activities of daily living (e.g., bathing, dressing, eating, toileting, medication administration, but not bedridden).
- **Grade 4**: Life-threatening, requiring urgent intervention.
- **Grade 5**: Death related to the AE.

(5) **Investigator Responsibilities During SAE Follow-Up**

Investigators must conduct appropriate examinations and treatments for SAEs based on clinical judgment, including necessary clinical laboratory tests and physical examinations. Any results from these examinations or additional updated information related to the SAE must be reported in follow-up reports, adhering to the same timeline and process as the initial report.

IX. Data Management

1. Data Management

(1) Investigators must ensure that data are authentic, complete, and accurate.

(2) Any corrections to trial records must be made by striking through the original entry, noting the corrected data alongside, providing a reason for the change, and including the investigator's signature and date. Original records must not be erased or obscured.

(3) Laboratory test items must be comprehensive and complete.

2. Data Recording and File Storage

Data related to participants in the Case Report Form (CRF) must be recorded using participant codes, and participants can only be identified by their code or initials.

This trial uses Excel for data management. The process includes data entry, verification against source data, resolution of quality control data queries, and finally, data locking and export. After confirming that there are no outstanding data issues, all parties sign the database lock request form, and the data administrator locks the database. Once locked, the data administrator exports the analysis database and provides it to the statistical team for analysis. Locked data cannot be edited. Any issues identified after database locking must be addressed and corrected in the statistical analysis program upon confirmation.

X. Data Safety Monitoring

The clinical study will establish a data safety monitoring plan based on the level of risk. All adverse events (AEs) will be meticulously documented, appropriately managed, and followed up until resolved or stabilized. Serious adverse events (SAEs) and unexpected events will be reported promptly to the ethics committee, competent authorities, sponsor, and drug regulatory authorities as required. The principal investigator will periodically review all AEs cumulatively and, if necessary, convene investigator meetings to assess the study's risks and benefits. In double-blind trials, emergency unblinding may be performed to ensure participant safety and rights.

XI. Statistical Analysis

1. Sample Size Determination

Based on previous studies, the symptom relief rate for GERD patients undergoing ECCL is 97%. A non-inferiority margin of 0.25 is set, with an estimated loss to follow-up rate of 5%. It is calculated that each group requires 23 patients ($\alpha = 0.05$, $\beta = 0.20$).

2. Definition and Selection of Analysis Sets

- **Full Analysis Set (FAS)**: The set of all participants who are enrolled, receive at least one dose of the study intervention, and have at least one efficacy assessment.
- **Safety Set (SS)**: The set of all participants who are enrolled, receive at least one dose of the study intervention, and have at least one safety assessment.
- **Per Protocol Set (PPS)**: The subset of the FAS consisting of participants who complete the protocol-specified treatment without significant protocol violations.

3. Statistical Methods

The analysis will include the distribution of cases, demographic and baseline characteristics, treatment feasibility and safety analysis, and efficacy analysis.

4. **Statistical Software and General Requirements**

- All statistical analyses will be performed using SPSS v26.
- Continuous data will be described using mean, standard deviation, median, maximum, and minimum values.
- Categorical data will be described using frequencies and percentages.
- Primary endpoints (safety, efficacy, post-procedure outcomes, and complications) will be analyzed using the chi-square test.

XII. Ethical Principles and Requirements for Clinical Research

The clinical study will adhere to the Declaration of Helsinki by the World Medical Association and the *Ethical Review Measures for Biomedical Research Involving Humans* by the National Health and Family Planning Commission of the People's Republic of China, among other relevant regulations. Specifically, the study will implement principles and requirements related to informed consent, privacy protection, provision of free research participation and compensation, risk control, protection of vulnerable participants, and compensation for research-related harm. Before the study begins, the trial protocol must be approved by the Ethics Review Committee. Prior to enrollment, investigators are responsible for fully and comprehensively explaining the study’s objectives, procedures, and potential risks to participants or their legal representatives, and obtaining written informed consent. Participants should be informed that their participation is entirely voluntary, that they may refuse to participate or withdraw at any stage of the study without facing discrimination or retaliation, and that their medical care and rights will not be affected. The informed consent form must be retained as part of the clinical study

documentation, ensuring the protection of participants' personal privacy and data confidentiality.

XIII. Study Timeline

- **June 2025 – June 2026**: Complete participant recruitment, randomization, and treatment.
- **July 2026 – June 2027**: Complete follow-up and statistical data analysis.
- **July 2027 – June 2028**: Complete manuscript writing.

XIV. References

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