STATISTICAL ANALYSIS PLAN

A PROSPECTIVE, MULTI-CENTER, RANDOMIZED CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF TWO TYPES OF ABSORBABLE SURGICAL SUTURES IN THE SUTURING OF THYROID SURGERY INCISION

ESC-201702

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

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TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol ESC-201702. It describes the data to be summarized and analyzed, including specifics of statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated 30/Sep/2019.

2. STUDY OBJECTIVES

The primary objective of this study is to evaluate the efficacy and safety of two types of absorbable surgical sutures - [redacted] Knotless Plus Tissue Control Device and [redacted] Knotless Tissue Control Device (hereinafter referred to as [redacted] and [redacted]) used in thyroid surgery to suture surgical incision.

For the primary efficacy endpoint, the study aims to demonstrate the non-inferiority of each of the two types of absorbable surgical sutures to the control group with respect to achieving Grade A healing of surgical incision(success).

3. STUDY DESIGN

This is a three-arm prospective, multi-center, randomized controlled study comparing the efficacy (non-inferiority tests) and safety of [redacted] and [redacted] to the control group [redacted] with [redacted]) in soft tissue suturing in subjects who undergo thyroid surgery.

In China, a total of approximately 501 subjects undergoing thyroid surgery in approximately 10 study sites will be enrolled into the study. Each site should enroll no more than 125 subjects (25% of the total number).

Prior to surgery, subjects will be randomized to the investigational group 1 ([redacted]), investigational group 2 ([redacted]) or the control group according to the allocation ratio of 1:1:1 using central randomization. The primary efficacy endpoint is the proportion of subjects achieving Grade A wound healing (success) of surgical incision in each group. A blind assessment will be performed on the wound healing status by independent Central Imaging evaluators on Day 5-7 post-surgery using the imaging data (a picture of complete neck anterior view, covering full length of the incision).

The subjects will be followed up on Day 5-7 and Day 28-35 post-surgery.

A schedule of study activities is included in section 7.2.1 of the study protocol. In addition, the study procedures and evaluations performed at each visit are included in section7.2.3 of the protocol.

4. PLANNED ANALYSES

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. FULL ANALYSIS SET (FAS)

FAS consists of all the enrolled subjects who were randomized and at least post-baseline effectivenenss endpoint evalution.

5.2. PER PROTOCOL SET (PP)

PP (evaluable) Set contains all the subjects in the FAS who have no major protocol deviation, have data available for primary efficacy endpoint and do not meet any of the following criteria:

o Subject undergoes any of the following procedures, in addition to thyroidectomy：

1、Any surgical procedure which require additional neck incisions or extend the original incision;

2、Cervical lymph node dissection (except the dissection of lymph nodes in the VI area);

3、Other unplanned surgical procedures (except the procedure that the investigator doesn't think it will affect the original incision's healing)

- Subject's intraoperative frozen pathology or postoperative paraffin section pathology suggests anaplastic thyroid cancer;

- Subject receives any surgical procedures that lead to re-opening of the cervical incision during the period from the wound closure to the completion of study, except for surgeries related to surgical incision complication or study device.

5.3. SAFETY SET

Safety Set contains all the enrolled subjects who receive surgery, product use, and at least post-baseline follow up

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the surgical procedure day (Day 1 is the day of surgical procedure) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. STATISTICAL TESTS

For the primary efficacy endpoint, for which two treatment group comparisons are performed as described in detail in section 13.1.1, the overall family-wise error rate is controlled at 0.025 level using the Holm's multiple comparisons procedure; confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.3. COMMON CALCULATIONS

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.2 or higher.

All continuous variables will be summarized by number of subjects, mean, standard deviation, median, minimum and maximum. All categorical data will be summarized by frequencies and associated percentages.

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

All study endpoints will be analyzed using the available data. Missing data for efficacy and safety endpoints will not be imputed.

8. OUTPUT PRESENTATIONS

The output module document provided with this SAP describe the manner in which data from this study will be presented and the format and content of the summary tables, figures and listings to be provided by [redacted].

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals, and protocol deviations, including inclusion and exclusion criteria, will be presented.

Protocol deviations will be summarized for Safety Set, including PD content and PD grading.

Subject disposition will be summarized with counts and percentages for each treatment group and in total. Categories summarized will include the number of subjects who signed informed consent, number of screen failures (with reasons), and the number enrolled, completed, and discontinued, as well as reasons for discontinuation. The summary of disposition will also include the number and percentage of subjects included in each analysis set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented will be summarized descriptively as described in section 6.3 for the Safety Set.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be summarized for this study:

- age (years) (age = date of signing informed consent - date of birth, rounded down),
- gender,

- ethnicity,
- height,
- weight,
- baseline EQ-5D-5L.

In addition, descriptive statistics for the Safety analysis set will be provided for, at a minimum, the following additional baseline characteristics: medical/surgical history, concomitant medications, and various laboratory data.

Surgery information such as procedure duration and OR time will also be summarized descriptively.

11. PRIOR MEDICAL /SURGICAL HISTORY

A pre-existing condition is one that is present at the start of the study and is to be reported as part of the subject's medical history. It must be reported as a new Adverse Event if the intensity, frequency, or the character of the condition worsens during the study treatment.

Relevant information in this section will be presented to the Safety set and described separately by treatment group.

MedDRA code will be used to summarize the medical/surgical history according to System Organ classification (SOC) and Preferred Term (PT).

12. CONCOMITANT MEDICATIONS

Medications will be presented for the Safety Set.

Concomitant medications used within the period from 7 days prior to the signing of ICF to the end of the study will be documented, excluding medications for surgical anesthesia.

13. EFFICACY OUTCOMES

13.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is defined as the proportion of subjects achieving Grade A healing (success) of surgical incision in each group.

13.1.1. SAMPLE SIZE CALCULATION

One hundred fifty (150) evaluable subjects per study arm will achieve 80% power to detect a non-inferiority margin difference in group proportions of -0.05 for each of the two comparisons using a Pearson Chi-square test with a one-sided significance level of 0.0125. The proportion of successes in the Control group is assumed to be 0.98. The proportion of successes in Test group [redacted] or [redacted]) is assumed to be 0.93 under the null hypothesis of inferiority, presented in section 13.1.2. The power was computed for the case when the actual proportion of successes in the Test group is 0.98.

To account for a potential 10% dropout rate, approximately 167 subjects per arm will be enrolled, for a total of approximately 501 subjects.

13.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

This is a non-inferiority trial with two treatment group comparisons, [redacted] versus control group, and [redacted] versus control group. The overall family-wise error rate is controlled at 0.025 level

using the Holm's multiple comparisons procedure. The expected proportion of successes is 0.98 for all the three groups.

For each of the two comparisons, the statistical hypotheses for testing the non-inferiority of the investigational group to control are presented as follows:

H_0: $P_T - P_C \leqslant -0.05$ tested against the alternative hypothesis

H_a: $P_T - P_C > -0.05$.

P_C is the proportion of successes (Grade A healing) in the control group and PT is the proportion of successes in each of the investigational groups (1 and 2).The proportion of subjects with Grade A healing will be summarized for each treatment group and will be calculated as the number of subjects with Grade A healing divided by the total number of subjects randomized to that treatment who had the surgical wound closed using the randomized suture. Within-treatment group, two-sided 95% confidence intervals for the proportions of successes will be provided using the Clopper-Pearson method.

For the primary endpoint analysis, the Holm's step-down procedure will be used. For each of the two group comparisons, the p-value associated with the non-inferiority test will be calculated using the Normal approximation Z (pooled) statistic. If the smaller p-value is smaller than 0.0125, then the null hypothesis associated with this p-value will be rejected and it will be concluded that the associated Test product is non-inferior to Control; subsequently, the larger p-value will be compared to 0.025 in order to test the non-inferiority of the other Test product to Control. If the smaller p-value is larger than 0.0125, then neither of the null hypotheses can be rejected and it will be concluded that, for both investigational devices, the study failed to demonstrate non-inferiority to Control.

The primary endpoint will be analyzed using the Full Analysis Set (FAS) and Per-Protocol (PP) sets. The PP analysis will be considered the primary analysis, while the FAS analysis will be considered supportive.

13.2. SECONDARY EFFICACY ENDPOINT

The following secondary efficacy endpoints are included:

13.2.1. INCISION SUTURING TIME

Defined as the time required from the first needle insertion for stitching ribbon muscles to the completion of intradermal suture (min);

13.2.2. MODIFIED HOLLANDER WOUND EVALUATION SCALE

Assessed by Imaging Center evaluators using pictures, including: a picture of complete neck anterior view containing full length of the incision, a picture taken parallel to the incision plane, a picture taken at a 45° angle to the incision plane, and incision lateral view pictures of both sides (one for each);

13.2.3. POSTOPERATIVE INCISION PAIN SCORE

VAS scale, see protocol Annex 4-1;

13.2.4. HEALTH RELATED QUALITY OF LIFE SCALE (EQ-5D-5L)

Subjects are required to select the most appropriate levels in 5 aspects to determine their health status (see protocol Annex 5):

- Motility
- Self care

- Daily activities
- Pain/discomfort
- Anxiety/Depression.

Actual values and the change from baseline to each scheduled visit in test results will be summarized for the FAS by treatment group and scheduled visit.

13.2.5. Analysis of Secondary Efficacy endpoints

The secondary efficacy endpoints will be summarized descriptively by treatment group and overall, as described in section 6.3, using the FAS. No inferential statistics will be generated for secondary efficacy endpoints.

14. Safety Endpoints

All outputs for safety endpoints will be based on the Safety Analysis Set.

Incidence of postoperative SSI、ASEPSIS score (only assessed in subjects with confirmed SSI)、Incidence of incisional wound separation or wound dehiscence requiring intervention、Incidence of delayed incisional wound healing events、Incidence of other AEs、and Product complaints will be summarized descriptively by treatment group and overall.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

The incidence of AEs will be assessed according to the classification of event and summarized descriptively by treatment groups. Incidence of AEs will also be assessed by onset time (intraoperative or postoperative), relationship to study surgical procedure, relationship to the study device, severity, and seriousness.

The specific safety endpoint incidences and other adverse events will be summarized descriptively in each treatment group and overall by presenting the number and percentage of subjects experiencing the occurrence of each event.

14.1. Adverse Event

AE is an untoward medical occurrence during the clinical study and which does not necessarily have a causal relationship with the study medical device.

An overall summary of number and percentage of subjects within each of the categories described in the sub-section below, will be provided as specified in the output module document.

Listings will include all AEs.

14.1.1. ALL AEs

Incidence of AEs will be presented by SOC and PT and also broken down further by maximum severity and relationship to study device.

14.1.1.1.Severity

Severity is classified as mild/moderate/severe (increasing severity). AE with a missing severity will be classified as severe. If a subject reports a AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

14.1.1.2.Relationship to Study Device

Relationship, as indicated by the Investigator, is classified as Unrelated, Possibly unrelated, Possible,

Probable, or Definitely Related (increasing severity of relationship). A ”related” AE is defined as a AE with a relationship to study device as ”possible”, ”probable”, or “definitely related”” . AEs with a missing relationship to study device will be regarded as ”probable”. If a subject reports the same AE more than once , the AE with the worst-case relationship to study device will be used in the corresponding relationship summaries.

14.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as ”Serious” on the Adverse Events page of the (e)CRF. A summary of serious AEs by SOC and PT will be provided.

In addition, the incidence of SAEs related to the study device will be summarized.

14.1.3. ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events which are recorded as ”Fatal” on the Adverse Events page of the (e)CRF. A summary of AEs leading to death will be provided.

14.2. DEVICE DEFECTS

Detailed information will be provided in listings.

14.3. PHYSICAL EXAMINATION

Detailed information will be provided in listings.