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Document Cover Page

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Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial Release	Haiying Lin, Principal Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
CBCT	cone-beam computed tomography
CIP	clinical investigation plan
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	ethics committee
ENB	electromagnetic navigation bronchoscopy
EWC	extended working channel
GCP	good clinical practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
ISO	International Organization for Standardization
IV	intravenous
MHLW	Ministry of Health, Labour, and Welfare
RDC	remote data capture
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SBRT	stereotactic body radiation therapy
USADE	unanticipated serious adverse device effect

- For baseline indicator variables, “unknown” responses will be counted as not having the characteristic and will be included in the denominator. Missing values will not be counted in rate denominators.

- Days to (event) = (event) date – procedure date.

3. Introduction

This statistical analysis plan provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the study. The proposed methods and approaches to the data analysis should be viewed as flexible if the data suggest and warrant deviations from this plan. However, any deviations from this analysis plan must be substantiated by a sound statistical rationale and documented in the final clinical study report. This statistical analysis plan (SAP) is based on version 3.0 of the protocol dated June 20, 2018. If there is CIP update(s), an assessment will take place to determine if any updates to the CIP require updates to the SAP.

4. Study Objectives

The primary objective of this prospective, single-arm, multicenter, non-randomized study is to characterize the safety of the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology device in subjects undergoing lung ablation procedures.

The primary endpoint is the composite rate of adverse events related to the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology through 1-month follow-up.

The following secondary endpoints will be evaluated:

- Composite rate of serious adverse events related to the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology through 1-month follow-up.
- Composite rate of all adverse events related to the procedure or study devices through 1-month follow-up.
- Composite rate of all serious adverse events related to the procedure or study devices through 1-month follow-up.
- Patient satisfaction and pain (Bronchoscopic Ablation Patient Pain and Satisfaction Survey)
- Quality of life (EQ-5D Scale)
- Technical success
- Technique efficacy

5. Investigation Plan

This is a prospective, single-arm, multicenter, non-randomized study. Up to 3 sites in up to 3 countries will enroll up to 30 subjects in total. The study is designed to characterize the safety and performance of the bronchoscopic ablation procedure using the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology.

Inclusion Criteria:

1. Subject is ≥ 18 years of age

2. Subject has provided informed consent

3. Subject is able and willing to comply with the study follow-up schedule

4. Subject has a definitive diagnosis of cancer in the lung

5. Target nodule is ≤ 30mm in maximum diameter

6. There is ≥ 5mm of nodule-free lung parenchyma between target nodule and pleura or fissure

7. Subject is a candidate for an elective electromagnetic navigation bronchoscopy (ENB) procedure

8. Subject is a candidate for an elective lung ablation procedure according to standard of care and product Instructions for Use

9. Subject is not a candidate for lung surgery or refuses lung surgery

10. Subject is not a candidate for stereotactic body radiation therapy (SBRT) or refuses SBRT

Exclusion Criteria:

1. Target nodule is abutting main stem bronchus, main pulmonary vasculature, esophagus and/or trachea

2. Patients currently diagnosed with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage IV emphysema

3. Female subjects who are pregnant or nursing as determined by standard site practices

4. Subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study

5. The investigator determines that participation in the study may jeopardize the safety or welfare of the subject

6. Determination of Sample Size

The sample size of this study is not based on power calculations of a statistical hypothesis test. Up to 30 subjects will be enrolled at up to 3 sites in up to 3 countries.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

After being informed of the nature of the study, the subject will sign a written informed consent form (ICF) that has been approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) of the respective clinical site. The point of enrollment is defined as the insertion of the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology into the EWC, rather than at the time of informed consent.

Subjects will be evaluated at baseline, procedure and 1 month, as detailed in Table 1 below. All study data will be collected on the appropriate subject eCRFs.

Table 1. Table of Assessments

	Baseline (Day -30 to Day 0)	**During the Procedure and Immediately Post- Procedure**	**1-Month Follow-up (20 to 40 Days Post- Procedure)**
Subject demographics	X		
Medical history (Lung Diagnoses, Previous Lung procedures, Lung function tests, etc.)	X		
Eligibility assessment	X	X	
Nodule characteristics		X	
Procedural information		X	
Adverse event assessment		X	X
Imaging	X*	X	X
Concomitant medications	X	X	X
Quality of life survey (EQ-5D)	X		X
Bronchoscopic Ablation Patient Pain and Satisfaction Survey			X

*Standard-of-care CT scan performed prior to consent.

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables. For subjects exiting the study, the reason for termination will be presented.

7.1.2 Analysis Sets

The point of enrollment is defined as the insertion of the EmprintTM Ablation Catheter Kit with ThermosphereTM Technology into the EWC. Unless otherwise specified, analysis of reported outcomes will include all available data for all enrolled subjects.

7.2 General Methodology

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- In general, data for all study subjects combined will be presented. Individual data will be presented in subject listings.
- Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.
- All summary tables will include the analysis population sample size (e.g., number of subjects, nodules, or devices).
- Baseline values will be defined as those values recorded prior to the study procedure (i.e. Day -30 to Day 0), in general.
- Change from baseline will be calculated as follows:

  Change = Post-baseline value - baseline value.
- Date variables will be formatted as DDMMMYYYY for presentation, for example, 01JAN2018.
- Adverse events for all enrolled subjects will be collected and reported. For adverse event reporting, which includes the primary and secondary safety endpoints, the primary analysis will be based on subject counts (e.g., the number and percentage of subjects with event among the total number of subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x subjects. For example, the data of 2% (20/1000) [38] indicates that a total of 38 events occurred in 20 subjects out of a total of 1000 subjects (2%).

- SAS® Version 9.4 or higher, or other widely accepted statistical or graphical software will used for all data analyses.

7.3 Handling of Missing Data and Dropouts

Due to the post-market and observational nature of the study, no imputation or other adjustment techniques are planned for missing data in the primary and secondary endpoints, if any. All available data from enrolled subjects will be reported.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Baseline Demographics

Subject demographic examples include:

- Age
- Gender

Continuous variables will be summarized with number of subjects (n), mean, standard deviation, median, and ranges. The frequency distributions (counts and percentages) will be given for categorical data.

7.4.2 Risk Factors

Risk factor examples include:

- Nodule size from Pre-Procedure CT
- Lobe location
- Lung Zone
- Bronchus sign present on CT

Number and percentages of subjects with each specific risk factor will be provided.

7.4.3 Medical and Surgical History

Medical and Surgical History examples include:

- History or Presence of Asthma/COPD/Tobacco Use
- Primary Cancer Diagnosis

Number and percentages of subjects with each Medical History and Surgical procedure type will be provided.

7.5 Procedure Characteristics

Procedural characteristics examples include:

- Nodule Size on Day of Procedure
- Type of anesthesia
- Procedure time
- Nodule visible on fluoroscopy
- Total number of fluoroscopy sweeps
- Total number of CBCT sweeps
- Total number of standard CT images
- Total number of X-ray images
- Total radiation dose from entire procedure
- Average ablative margin

Continuous variables will be summarized with number of subjects (n), mean, standard deviation, median, and ranges (for procedure time, 1st and 3rd quartiles will be provided as well). The frequency distributions (counts and percentages) will be given for categorical data.

7.6 Interim Analyses

There are no pre-planned interim or subgroup analyses. Any post-hoc subgroup analyses will be exploratory in nature for the purpose of evaluating the safety and performance of the study device under various clinical conditions.

7.7 Evaluation of Objectives

This section will discuss the tabulation and analysis of the study endpoints, including primary and secondary endpoints. The primary and secondary safety endpoints will be summarized using frequency measures in the format of p% (x/N) [e], with p and x being the percentage and number of subjects with event, respectively, N being the number of all subjects with ENB index procedure, and e being the total number of events occurred in the x subjects. A 2-sided 95% exact binomial confidence interval for the primary endpoint will also be provided.

7.7.1 Primary Endpoint

The primary endpoint is the composite rate of adverse events related to the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology through 1-month follow-up.

A subject has a primary endpoint if all conditions below are met:

- if the question of "Is the AE related to the Emprint Ablation Catheter?" is checked "YES" (in the CEC_NC CRF), and

7.7.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

7.7.2.1 Composite rate of serious adverse events related to the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology through 1-month follow-up.

It is calculated as follows:

- if the question of "Is the AE serious?" is checked "YES" (in the CEC_NC CRF), and
- if the question of "Is the AE related to the Emprint Ablation Catheter?" is checked "YES" (in the CEC_NC CRF), and

7.7.2.2 Composite rate of all adverse events (AEs) related to the procedure or study devices through 1-month follow-up.

It is calculated as follows:

- if at least one of the following questions is checked "YES" (in the CEC_NC CRF)
  - "Is the AE related to the Emprint Ablation Catheter?", or
  - "Is the AE related to the ENB procedure?", or
  - "Is the AE related to the ablation procedure?", or
  - "Is the AE related to anesthesia for the study procedure?", or
  - "Is the AE related to the superDimension Navigation System?", or
  - "Is the AE related to the Positioning Tool?", and

7.7.2.3 Composite rate of all serious adverse events (SAEs) related to the procedure or study devices through 1-month follow-up.

It is calculated as follows:

- if the question of "Is the AE serious?" is checked "YES" (in the CEC_NC CRF), and
- if at least one of the following questions is checked "YES" (in the CEC_NC CRF)
  - "Is the AE related to the Emprint Ablation Catheter?", or

- "Is the AE related to the ENB procedure?", or
- "Is the AE related to the ablation procedure?", or
- "Is the AE related to anesthesia for the study procedure?", or
- "Is the AE related to the superDimension Navigation System?", or
- "Is the AE related to the Positioning Tool?", and

7.7.2.4 Patient satisfaction, pain and level of breathlessness (Bronchoscopic Ablation Patient Pain, level of breathlessness, and Satisfaction Survey)

For each of the question in the PT_SAT CRF, the data will be summarized using frequency measures in the format of p% (x/N) with p and x being the percentage and number of subjects with "YES" answer to evaluation questions and N being the number of all subjects who fill the satisfaction evaluation. Continuous variables (e.g. Pain or discomfort level subjects experienced because of the bronchoscopic ablation procedure) will be summarized with number of subjects (n), mean, standard deviation, median, and ranges.

7.7.2.5 Quality of life (EQ-5D Scale)

EQ-5D Index and EQ Visual Analogue Scale (VAS) at baseline and 1 month in the EQ5D CRF will be summarized with number of subjects (n), mean, standard deviation, median, and ranges. The mean, standard deviation, median, and ranges for changes from baseline may also be provided.

7.7.2.6 Technical success

Technical success: An evaluation of whether the lung nodule was treated according to the study protocol as determined at the immediate post-procedural timepoint. This is in contrast to procedures in which the protocol could not be executed completely, either for technical reasons or for reasons related to comorbid disease.

In the Procedure CRF, if the question of "Was there technical success, i.e. nodule treated according to protocol?" is checked "YES", it is considered technical success.

The endpoint will be calculated per subject and in the format of p% (x/N), with x being the number of subjects with technical success, and N being the number of all subjects enrolled.

7.7.2.7 Technique efficacy

Technique efficacy: An evaluation of whether the lung nodule was effectively ablated. Evaluates whether complete ablation of the nodule was achieved as evidenced by imaging follow-up 1-month post-procedure (including a window of 20-40 days post-procedure).

In the FUP CRF, if the question of "Based on imaging, was complete ablation of the nodule achieved?" is checked "YES", it is considered that the lung nodule was effectively ablated.

The endpoint will be calculated per subject and in the format of p% (x/N), with x being the number of subjects whose complete ablation of the nodule achieved, and N being the number of subjects with performed follow-up imaging.

7.8 Safety Evaluation

7.8.1 Definitions of Adverse Events

7.8.1.1 Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

7.8.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is an AE that has

1. Led to death,

2. Led to serious deterioration in the health of the subject, that either resulted in

   a. A life-threatening illness or injury, or

   b. A permanent impairment of a body structure or a body function, or

   c. In-patient or prolonged hospitalization, or

d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

NOTE 1: This includes device deficiencies that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered an SAE.

7.8.1.3 Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of the investigational medical device (the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology).

NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

7.8.1.4 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is a serious adverse event related to the study device which by its nature, incidence, severity or outcome has not been identified in the current version of the Risk Management Report.

7.8.1.5 Adverse Event Relationship Classification

The following definitions will be used to assess the relationship of the AE to the investigational medical device (the Emprint™ Ablation Catheter Kit with Thermosphere™ Technology), accessory devices, or study procedures:

• Not related: Relationship to the device or procedures can be excluded

• Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

• Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or

concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

• Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

For the AE relatedness reporting, the degree of causality's term "not related" will be considered as not related to the device or procedures, and terms "unlikely", "possible" or "probable" will be considered as related to the device or procedures.

7.8.2 Reporting of Adverse Events

All summaries of adverse events will be based on events that occurred during the study. Adverse event reporting is per Medical Monitor adjudication for those that require Medical Monitor adjudication, and the remaining events will be per site reported data.

Adverse events will be mapped to preferred terms (i.e. Dictionary-Derived Term) and Body System or Organ Class using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects experiencing adverse events will be summarized by system organ class and preferred term.

7.9 Device Deficiencies Analyses

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Device deficiencies will be summarized in frequency measures by device type and device deficiency category. For the device deficiencies that result in SAEs, a detailed subject listing will be provided including subject number, device type, device deficiency category, deficiency description, deficiency time, device deficiency outcome, SAE description, action taken, and event outcome.

7.10 Protocol Deviation

A protocol deviation is defined as any divergence from the study protocol. The total number of protocol deviations and total number of subjects with deviations will be provided by deviation type for all enrolled subjects.

8. Validation Requirements

Level II validations (i.e. the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output) will be performed for analysis outputs.