Statistical Analysis Plan

Clinical Investigation Plan Title	EMPRESS: The EMPrint™ Ablate and RESect Study in Patients with Metastatic Lung Tumors
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Document Release	Mei Jiang, Principal Statistician
2.0	• Revise and reformat based on new SOP	Shannon Song, Principal Statistician
3.0	• Redacted proprietary information to post with results on CT.gov in accordance with Final Rule	Briston Gregg, Clinical Research Coordinator III

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect; Adverse event related to the use of an investigational medical device, including adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, as well as any event resulting from use error or from intentional misuse of the investigational medical device.
AE	Adverse event; 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 device. This includes events related to the investigational device or the comparator and procedures involved.
ASADE	Anticipated serious adverse device effect; an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report (R0042262).
CIP	clinical investigational plan
CRF	Case report form
CT	computed tomography
Device deficiency	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.
EC	Ethics committee (see IEC)

eCRF	Electronic case report form
H&E	Hematoxylin and eosin stain routinely used to evaluate the structural integrity of cells
IEC	Institutional ethics committee (see EC)
IFU	Instructions for Use; a manual or document accompanying a technical device that describes the directions by which the device should be used, applied, etc.
Investigative Site	An approved, participating study center/institution
Investigator	Either a principal, coordinating or sub-investigator, unless otherwise specified
IRB	Institutional Review Board
MWA	microwave ablation
NADH	β-nicotinamide adenine dinucleotide, reduced; assay used to determine cell viability
OR	Operating Room
RDC	Remote data capture; internet-based data entry system used to enter and store study data points
RTP	remote temperature probe
SADE	Serious adverse device effect; adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SAE	Serious adverse event; an adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

TEAE	Treatment-emergent adverse event; any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.
USADE	Unanticipated serious adverse device effect; serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

3. Introduction

The EMPRESS study is a post market prospective, non-randomized, single-arm, multicenter study, designed to demonstrate dose response of the Emprint™ Ablation System using a percutaneous approach in patients with metastatic or primary lung tumors.

This document 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 2 of the protocol dated February 24, 2015.

4. Study Objectives

The primary objective of this post-market clinical study is to demonstrate technical performance of a CT-guided percutaneous microwave ablation system in patients with metastatic lung tumors or recurrent primary lung tumors.

Following CT-guided ablation of the tumor, a CT image will be performed to evaluate dose response. The ablation zone will then be resected as part of the standard surgical procedure and the tissue specimen will be examined using histology to determine the completeness of tumor ablation.

5. Investigation Plan

This will be a post market prospective, non-randomized, single-arm, multicenter study.

Ablations will be carried out using a percutaneous approach at a dose (power and time setting) selected during procedure planning. The procedure planning application will be used as an adjunct planning tool. While the physician prescribes the dose, the Emprint™ Procedure Planning Application overlays the 3-dimensional predicted ablation zone on the patient CT images, facilitating visualization of the predicted ablation zone relative to the target tumor. Once the ablation procedure is complete, the scheduled surgical tumor resection will be performed.

6. Determination of Sample Size

No formal sample size estimates were conducted for this post-market, prospective, non-randomized,

single-arm, multicenter study. Up to 30 subjects who are scheduled for resection of metastatic or primary lung tumor(s) will be enrolled. Ablations will be carried out using a percutaneous approach at a dose (power and time setting) selected during procedure planning. Up to 10 study sites in the United States and Europe will participate in this trial.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables. The following information will be provided by study site:

- Number and percentage of screen failures
- Number and percentage of enrolled subjects
- Number and percentage of subjects who have completed the Emprint™ ablation procedure
- Number and percentage of subjects who have completed the Emprint™ ablation procedure and the Primary Endpoint
- Number and percentage of subjects who have completed the Emprint™ ablation procedure and the Secondary Endpoint
- Number and percentage of subjects who have completed the postoperative evaluation / end of study Visit
- Number and percentage of subjects who exited the study, overall and by study exit type

7.1.2. Clinical Investigation Plan (CIP) Deviations

A CIP deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the CIP. Deviations shall be reported regardless of whether medically justifiable or taken to protect the Subject in an emergency.

Except a change that is intended to eliminate an immediate hazard to a Subject, the protocol will be followed as described. Subject specific deviations and non-Subject specific deviations will be reported. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

7.1.3. Analysis Sets

In general, data analysis will be conducted on all subjects who are enrolled in the trial and undergo the ablation procedure using the Emprint™ system.

Intent-To-Treat (ITT): subjects enrolled into the study.

Modified ITT (MITT): ITT subjects who completed the ablation procedure. If all ITT subjects completed the ablation procedure, then the ITT population is the same as the MITT population.

Additional analysis sub-populations may be defined per scientific research need.

7.2. General Methodology

Descriptive statistics will be generated for pre-intervention demographics, procedural characteristics, and follow-up data collected. Categorical variables will be analyzed using frequency, incidence, and event rate. For continuous variables collected in the study, data will be summarized using mean, median, standard deviation, and range.

7.3. Center Pooling

This is a multi-center clinical study, with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. 30 subjects will be enrolled from up to 10 clinical sites, all the data will be pooled for reporting.

7.4. Handling of Missing Data and Dropouts

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure.

When calculating rates of adverse events, missing and partial dates will be handled as follows. If the entire adverse event start date is missing then the procedure date will be used for the start date. If the month and the day of the month are missing but the year is available and the year is the same as the year of the procedure then the procedure date will be used for the start date. If the year is greater than the year of the procedure then January 1st will be used for the month and day of the start date. If the day is missing, but the month and year are available, then the 1st will be used as the day of the start date unless the imputed date would before the procedure in which case the procedure date will be used for the start date of the adverse event.

For baseline categorical 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.

7.5. Adjustments for Multiple Comparisons

Not applicable since no statistical test will be performed on the primary or secondary endpoint.

7.6. Demographic and Other Baseline Characteristics

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.

7.6.1. Baseline Demographics

The following subject demographic data will be summarized.

- Age
- Gender
- Ethnicity
- Race
- Height
- Weight

7.6.2. Smoking History

The following smoking history data will be summarized:

- History of tobacco use (Yes/No, if yes, current/former)
- Tobacco use: type of tobacco, duration of use, # of units, and use frequencies

7.6.3. Cancer Diagnosis

The following cancer diagnosis data will be summarized:

- Primary cancer type
- Tumor pathology
- Months since primary cancer diagnosis
- Target tumor type
- Location of target tumor
- Prior cancer treatments
    - Cancer type
    - Years of since previous cancer diagnosis
    - Cancer treatment
    - Months since last cancer treatment

7.6.4. Medical History

The following medical history data will be summarized:

- Has the patient ever had surgery in the thoracic space? (unrelated to Lung Cancer treatment)
- Previous lung disease diagnosis

7.7. Treatment Characteristics

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

7.7.1. Planning Application

Planning application characteristics:

- Axial two-dimensional measurement - maximum axial length
- Axial two-dimensional measurement - perpendicular axial length associated within maximum axial length
- Planned antenna point of entry (intercostal space)
- Planned approach
- Planned ablation time
- Planned ablation power
- Planned tip distance
- Planned insertion depth
- Target tumor width (X)
- Target tumor height (Y)
- Target tumor depth (Z)
- Calculated target tumor volume from planning application
- Predicted ablation zone width (X)
- Predicted ablation zone height (Y)
- Predicted ablation zone depth (Z)
- Predicted ablation zone volume
- Predicted minimum margin
- Predicted maximum margin

7.7.2. Ablation Procedure

Procedural characteristics:

- Duration of anesthesia (min)
- Type of anesthesia
- Duration of antenna placement (min)
- Antenna length
- Number of passes through the gantry for placement
- Actual approach
- Duration of ablation time (min)
- Actual ablation power

7.7.3. CT Imaging

CT imaging characteristics:

- Pre-procedure image quality
- Lesion location
- Longest axial diameter
- Perpendicular diameter
- Tumor volume
- Critical structures within 10mm of tumor border
- Distance from tumor
- Intra-procedural image quality
- Radiating section of antenna of tumor center
- Tip to tumor margin
- Post-procedural image quality
- Ablation zone Width x
- Ablation zone Width y
- Ablation zone Depth z
- Tip distance
- Calculated ablation zone volume
- Needle depth
- Ablation zone shape

- Presence of cavitation
- Maximum margin
- Minimum margin
- Location of areas with margins less than 0.5mm

7.8. Interim Analyses

Interim analyses will be conducted once the first 15 tumors are ablated. The interim analyses will be performed by following the same principle defined in this statistical analysis plan.

7.9. Evaluation of Objectives

7.9.1. Primary Endpoint

The primary endpoint is dose response immediately post-procedure and prior to surgical resection and is defined as the percentage change from the predicted outcome to the actual outcome.

The predicted values are from the PLAN CRF:

- Predicted ablation zone width (X)
- Predicted ablation zone height (Y)
- Predicted ablation zone depth (X)
- Predicted ablation zone volume
- Calculated ablation zone volume (calculated from predicated X, Y, and Z value)

$$Calculated\ Ablation\ Zone\ Volume = \frac{4 * 3.14}{3} * \frac{Predicted\ Ablation\ Zone\ Width * Height * Depth}{8}$$

- The predicted ablation zone shape is the calculated ratio of predicted ablation zone width (X) and ablation zone height (Y)

$$Predicted\ \ Ablation\ Zone\ Shape = \frac{Predicted\ Ablation\ Zone\ Width}{Predicted\ Ablation\ Zone\ Height}$$

The actual values are from the IMAGE CRF:

- Width (X)
- Height (Y)
- Depth (X)
- Ablation zone volume

$$Calculated\ Ablation\ Zone\ Volume = \frac{4 * 3.14}{3} * \frac{Actual\ Ablation\ Zone\ Width * Height * Depth}{8}$$

- Ablation zone shape

$$Ablation\ Zone\ Shape = \frac{Ablation\ Zone\ width}{Ablation\ Zone\ height}$$

The percentage change (calculated as 100*(A-P)/P) (where P=predicted and A=actual) will be calculated for each of the following measurements:

- Ablation zone width (X)
- Ablation zone height (Y)
- Ablation zone depth (Z)
- Ablation zone volume
  - ✓ Predicated ablation zone volume vs actual ablation zone volume
  - ✓ Calculated ablation zone volume (calculated from predicated X, Y, and Z value) vs. actual ablation zone volume
- Ablation zone shape

For each of the above measurements, the percentage change will be summarized with number of subjects (n), mean, standard deviation, median, and ranges. Summary will be done for all target tumors combined and for each target tumor type (primary, recurrent, and metastatic).

7.8.2. Secondary Endpoint

Complete tumor ablation immediately post-procedure will be measured for each target tumor using histologic analysis to evaluate complete ablation at the cellular level.

All histology samples will be evaluated by a core laboratory. Both vital staining (Nicotinamide adenine dinucleotide (NADH) assay) and structural staining (hematoxylin and eosin; H&E) techniques will be used to evaluate cellular integrity within the ablation zone.

The histology data for the NADH assay is from the NADH Sample Analysis – Part 1 of the PATHOLOGY CRF:

- If the "Evidence of Complete Ablation" is checked Yes, it is complete tumor ablation
- If the "Evidence of Complete Ablation" is checked No and the "If No, Was Delayed Necrosis Achieved" is checked Yes, it is delayed necrosis
- If the "Evidence of Complete Ablation" is checked No and the "If No, Was Delayed Necrosis Achieved" is checked No, it is incomplete tumor ablation

The histology data for the H&E assay is from the H&E Sample Analysis – Part 2 of the PATHOLOGY CRF:

- If the "Evidence of Complete Ablation" is checked Yes, it is complete tumor ablation
- If the "Evidence of Complete Ablation" is checked No, it is incomplete tumor ablation

The number and percentage of tumors which achieve complete tumor ablation, delayed necrosis and incomplete tumor ablation for all target tumors combined and for each target tumor type (primary, recurrent, and metastatic) will be provided. The summary will be provided by NADH assay, H&E assay, and NADH and H&E combined.

7.10. Safety Evaluation

Adverse events for all enrolled subjects will be collected and reported. All reported adverse events will be presented based on the ITT population and tabulated by system organ class and preferred term. The incidence of peri-procedural and post-procedural events related to the actual procedure or the study device will be summarized and reported using counts, and percentages.

7.11. Health Outcomes Analyses

NA.

7.12. Changes to Planned Analysis

NA.

8. Validation Requirements

Primary and secondary endpoints will be validated by level I validation and the rest of the tables, listings and figures will be validated by level II validation.

Level I: The peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. Define the level of validation required for each objective or analysis output.

Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.