Statistical Analysis Plan (SAP)

< A Prospective Multicenter Study of Transbronchial Microwave Ablation Using Robotic-Assisted Bronchoscopy in Subjects with Oligometastatic Tumors in the Lung (POWER) >

Protocol Version: NEU_2020_03 V2.0 (18Aug2022)

SAP Version: V 1.0
SAP Version Date: Aug 1, 2023

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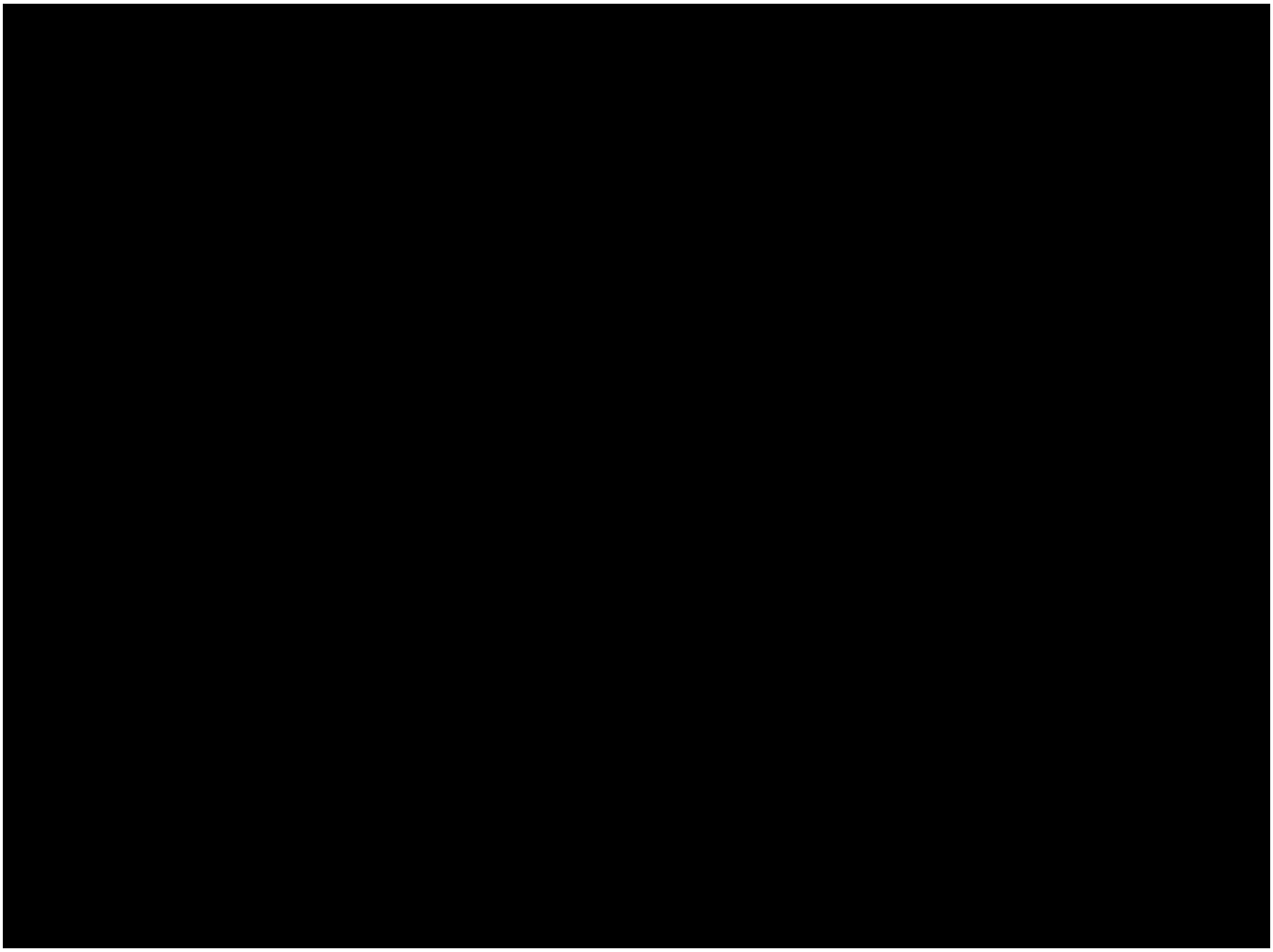
The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:



Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision

Abbreviations

AE	Adverse Event
CBC	Complete Blood Count
CBCT	Cone-Beam Computed Tomography
CHF	Congested Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DSS	Disease Specific Survival
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
HRQOL	Health-Related Quality of Life
ITT	Intent-to-Treat
LTP	Local Tumor Progression
LTPFS	Local Tumor Progression Free Survival
MWA	MicroWave Ablation
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
OUS	Outside the United States
PFS	Progression Free Survival
PFTs	Pulmonary Function Tests
PI	Principle Investigator
RFA	Radio Frequency Ablation
SAE	Serious Adverse Event

Table of Contents

1 Study Design

This is a prospective, multicenter, single-arm study of transbronchial microwave ablation using robotic-assisted bronchoscopy in adult subjects with oligometastatic tumors (≤ 2cm) in the lung, located in the outer two-thirds and not closer than 1cm to the pleura (including fissures), with colorectal, renal, or sarcoma histology.

Subjects with at least one oligometastatic tumor in the lung who meet all inclusion/exclusion criteria will have transbronchial microwave ablation performed using CBCT scan for probe guidance and confirmation. Subjects will be followed for 12 months following the first ablation procedure for safety and effectiveness outcomes.

Overall, the study will include up to 145 subjects across approximately 15 sites, where principal investigators will be licensed pulmonologists/interventional pulmonologists or thoracic surgeons who have completed at least 20 diagnostic cases using the MONARCH Platform including at least 5 cases using CBCT and completed the Sponsor-required FLEX MC training.

In this study, "target" tumors are defined as lung tumors that are treated with FLEX MC at the index ablation procedure (i.e., Visit 2). A subject may have a maximum of two target tumors. "Non-target" tumors are defined as lung tumors that are treated with FLEX MC during study follow-up after completion of the primary endpoint, Technique Efficacy assessments at Visit 3 (i.e., Visits 3-6). A subject may not have more than three total tumors treated with FLEX MC (including target and non-target tumors).

A central review committee of radiologists will independently review all CT scans (and other scans, as applicable) taken throughout the clinical study in an effort to standardize scan assessment and to minimize potential bias of the treating physician. Both the clinical site's radiographic assessment and the central review committee's assessment will be captured within the CRFs and reported within the final Clinical Study Report. The central review committee assessment for the following key endpoints will be used for the final analysis.

Assessment	**Visit 1** (Screening)	**Visit 2** (Ablation Visit)	**Visit 3** (30 days post-ablation)	**Visit 4** (3 months post-ablation)	**Visit 5** (6 months post-ablation)	**Visit 6** (12 months post-ablation)
Tumor size* (smallest and largest diameters)	X					
Ablation zone (smallest and largest diameters)		X				
Smallest minimal ablation margin		X				
Technical Success		X				

Technique Efficacy			X			
Local tumor progression				X	X	X
Other tumor progression (regional or distant)				X	X	X

*Tumor size, as analyzed by the central review committee, will be used for reporting purposes only. The investigator's assessment of tumor size will be used for inclusion/exclusion purposes.

The study will end when all enrolled and treated subjects have completed the 12-month, post-ablation follow-up period or have withdrawn consent prior to completion. The Sponsor may also stop or pause enrolling new subjects prior to reaching 145 subjects based on either safety events, regulatory feedback, or inability to enroll appropriate subjects.

Table 1: Schedule of Assessments

Visit No.	Visit 1	Visit 2			Visit 3	Visit 4	Visit 5	Visit 6	Unsched. Visit[21]
Visit	Screening	Pre-Procedure	Intra-Procedure	Post-Procedure	Follow-up	Follow-up	Follow-up	Follow-up	
Interval Windows	≤ 30 days pre-ablation	Day 0	Day 0	Day 0 - Discharge	30 days (-7 to +14 days)	3 months (±2 weeks)	6 months (±1 month)	12 months (±1 month)	
Standard Study Assessments									
Informed Consent	X								
Inclusion / Exclusion Criteria	X	X							
Demographics	X								
Medical / Surgical History[1]	X								
Concomitant medications[2]	X	X		X	X	X	X	X	X
Concomitant procedures	X	X		X	X	X	X	X	X
BMI	X								
Key Vitals[3]	X	X		X	X	X	X	X	
ECOG Status	X	X			X	X	X	X	
Pulmonary function tests (PFTs)	X					X	X	X	
Laboratory Assessments									
Pregnancy test[4]	X	X							
Coagulation tests[5]	X	X[6]							
CBC with differential	X								
Tumor markers/molecular profiling[7]	X								
Subject Report Outcome Assessments									
Numeric Pain Rating Scale	X	X		X					
Quality of Life Questionnaires[8]	X				X	X	X	X	
Ablation Assessments									
Ablation procedure details[9]		X							
Imaging Assessments									
Chest CT[10]	X[11]				X[12]	X	X	X	
Abdomen and Pelvis CT[10]	X[13]					X	X	X	

Visit No.	Visit 1	Visit 2			Visit 3	Visit 4	Visit 5	Visit 6	Unsched. Visit[21]
Visit	Screening	Pre-Procedure	Intra-Procedure	Post-Procedure	Follow-up	Follow-up	Follow-up	Follow-up	
Interval Windows	≤ 30 days pre-ablation	Day 0	Day 0	Day 0 - Discharge	30 days (-7 to +14 days)	3 months (±2 weeks)	6 months (±1 month)	12 months (±1 month)	
Imaging Assessments, Cont.									
Brain MRI[14]	X					X	X	X	
Extremity CT or MRI[15]	X					X	X	X	
Cone Beam CT			X[16]						
Technical Success			X						
Technique Efficacy					X				
Tumor Progression						X	X	X	
Safety Assessments									
Perioperative AEs[17]	X	X	X	X	X				
Other AEs						X	X	X	X
SAEs	X	X	X	X	X	X	X	X	X
Hospital-Related Assessments									
UB-04 Data[18]				X					
Length of hospital stay[19]				X					
Assess for hospital readmission[20]					X				

2 Treatment Assignment

All subjects enrolled in this study will be treated with the transbronchial ablation procedure using the NEUWAVE^{TM} FLEX MC Microwave Ablation System and Accessories.

3 Randomization and Blinding Procedures

This is an open-label, single-arm study. No randomization or blinding of treatment will be performed.

4 Interval Windows

Interval windows are provided in Table 1: Schedule of Assessments. No additional windows are planned for analysis purposes.

5 Levels of Significance

The following hypotheses will be evaluated in this study:

$$H_0: p \leq 0.80 \text{ vs.}$$

$$H_1: p > 0.8$$

where *p* represents the true 30-day Technique Efficacy rate of FLEX MC and 0.80 is the performance goal, which was determined through an internal systematic literature review and meta-analysis of microwave and radiofrequency ablation systems used in the treatment of lung tumors.

A one-sided significance level of 0.025 will be used to test the hypotheses above. If the lower bound of the confidence interval is above 0.8, then the following secondary endpoints will be provided with 95% confidence intervals at month 12, in addition to the descriptive statistics:

- Local Tumor Progression Free Survival,
- Progression Free Survival,
- Disease Specific Survival, and
- Overall Survival

No other formal hypothesis tests are planned for this study and estimation for all other endpoints will be provided descriptively.

6 Analysis Sets

Intent-to-treat Set (ITT) is defined as all enrolled patients with the FLEX MC ablation procedure attempted (i.e., microwave ablation initiated). The primary analysis of effectiveness endpoints and safety will be performed on the ITT. If more than 7 patients (5%) start the ablation but fail to complete ablation due to any reasons, all the secondary efficacy analyses will also be repeated under ITT set.

Full Analysis Set (FAS) is defined as all subjects who are enrolled in the study and successfully complete the FLEX MC ablation procedure. This will be used for effectiveness endpoints.

Per Protocol analysis Set is defined as all subjects who complete the FLEX MC ablation procedure and have no major protocol deviations. Primary endpoint and Technical Success analyses will be repeated for the Per Protocol Set.

7 Sample Size Justification

Establishment of the performance goal for Technique Efficacy was determined through performing a systematic literature review and meta-analysis to obtain a pooled estimate for MWA and RFA based on available published literature. Ovid MEDLINE®, Embase, and Evidence Based Medicine Reviews from January 1, 2005 to March 31, 2021 were searched to identify literature reporting on studies that included at least 20 adult subjects with NSCLC or lung metastases who were treated with MWA or RFA and reported on Technique Efficacy at a target of one-month post-ablation (up to a maximum of 3 months). Study designs included randomized controlled trials, comparative observational studies, and single-arm studies. Conference abstracts, studies with less than 20 subjects, and studies assessing salvage therapies were excluded.

A total of 19 studies of percutaneous ablation were included with random-effects and fixed-effects methodologies being applied to obtain a point estimate of average Technique Efficacy and corresponding 95% confidence interval.

Results from the representative set of MWA studies demonstrated a point estimate of average Technique Efficacy to be 89% with 95% confidence interval (81%, 94%). In consideration of the lower bound of the estimated confidence and a clinically meaningful minimum acceptable level of performance while recognizing that there may be some learning curve with the new technology and allowing for a modest region of indifference, a performance goal of 80% was established for this study.

Determination of the study sample size was then performed based on a power analysis where the null hypothesis being considered was H0: $p \leq 0.80$ against the alternative hypothesis of H1: $p > 0.80$, where p represents the true 30-day Technique Efficacy rate of FLEX MC and 0.80 is the performance goal. It is assumed that the expected Technique Efficacy rate observed for FLEX MC will be 0.90 and, therefore, a sample size of 137 subjects will provide greater than 90% power for evaluating the above hypotheses at a one-sided significance level of 0.025 using the Normal approximation to the Binomial distribution. Accounting for up to 5% dropout at the 30-day timepoint leads to a sample size of 145 subjects. This conservatively assumes one target tumor per subject.

At least 50% of the study population will be enrolled from sites in the United States.

8 Analyses to be Conducted

8.1 General Conventions

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, subject listings will also be used to present the data.

All results will be presented overall and by region to assess similarity of clinical results. For the primary and selected secondary endpoints, summary will also be presented by site.

8.2 Disposition of Study Subjects

Subject disposition will be summarized using counts and percentages. The number and percentage of subjects in each analysis set and the number and percentage of subjects completed and discontinued, along with the specific reasons for discontinuation, will be tabulated by region (US and OUS) and in total.

A listing of subjects who discontinued study participation will be provided.

8.3 Demographic and Baseline Characteristics

Demographic and baseline characteristic variables will be summarized descriptively. Demographic characteristics include age, gender, race, and ethnicity. Baseline characteristics to be summarized include:

- Smoking history

- BMI
- Key vitals (blood pressure, heart rate, and pulse oximetry)
- ECOG performance status
- Numeric pain rating scale
- EORTC QLQ-C30, QLQ-LC13
- CBC (complete blood count) with differential
- Coagulation tests – APTT and PT/INR
- Pulmonary function tests (PFTs) - Spirometry (e.g., FEV1, FVC, FEV1/FVC, FEF25-75, Peak Expiratory Flow, and Maximum Ventilation Volume), Diffusion Capacity (DLCO), Total Lung Capacity (TLC), Functional Residual Capacity (FRC), and Residual Volume (RV)
- Primary cancer diagnosis: sarcoma, renal or colorectal histology, stage, years since diagnosis, treatment for the primary cancer
- Pre-ablation lung tumor characteristics - number of tumors, target/non-target, location, size (average of long and short), distance from pleura

Ablation procedure related information will be listed.

8.4 **Medical History**

Targeted medical history (chronic obstructive pulmonary disease/emphysema, coronary artery disease/prior myocardial infarction, congestive heart failure, hypertension, pulmonary hypertension, diabetes, chronic renal insufficiency, liver cirrhosis, and other) will be summarized with counts and percentages.

Surgical/procedural history (lung related, primary tumor related, other) will be summarized.

8.5 **Protocol Deviations**

Protocol deviations will be assessed. Deviations that may impact the study inferences will be regarded major. Such deviations will be identified before final database lock.

The incidence of major protocol deviations, together with the corresponding deviation terms will be summarized. A listing of all major protocol deviations including subject ID, type of deviation, and reason will be provided.

8.6 **Concomitant Medications and Procedures**

Concomitant medications will be summarized and listed, as appropriate. Medications of interest (chemotherapies, immunotherapies, targeted therapies, anti-angiogenic therapies, other anti-cancer therapies or investigational agents) will also be summarized.

Concomitant procedural indications (prophylactic, adverse event, disease progression) will be summarized.

8.7 **Product Complaints**

Product-related complaints will be summarized by event timing (pre, intra, post procedure), device relation (Auris, NeuWave, both Auris/NeuWave, or Unknown), and AE association.

8.8 **Primary and Secondary Endpoint(s) and Associated Hypotheses**

8.8.1 Primary Endpoint(s) and associated hypotheses

Technique Efficacy is defined as the proportion of subjects with ablation of the target tumor(s) with the ablation zone completely overlapping or encompassing the entire target tumor(s) using CT imaging at 30 days (-7 to +14 days) post the original ablation procedure. If >1 target tumor, both tumors have to meet TE in order to consider TE for the subject.

The number and percentage of tumors achieving Technique Efficacy will be summarized and a 95% confidence interval will be estimated with the Wilson score confidence intervals as shown below. Hypothesis testing for the primary endpoint will be performed using the methodology described in the Section 5.

$$\left(\frac{\hat{p}+\frac{z^2_{\alpha/2}}{2n}-z_{\alpha/2}\sqrt{\frac{\hat{p}\hat{q}}{n}+\frac{z^2_{\alpha/2}}{4n^2}}}{1+\frac{z^2_{\alpha/2}}{n}},\ \frac{\hat{p}+\frac{z^2_{\alpha/2}}{2n}+z_{\alpha/2}\sqrt{\frac{\hat{p}\hat{q}}{n}+\frac{z^2_{\alpha/2}}{4n^2}}}{1+\frac{z^2_{\alpha/2}}{n}}\right)$$

Technique Efficacy (TE) at Visit 3 (30 days post-ablation) will be performed on observed data only and involving only target lesions. The TE rate is the number of subjects achieving TE divided by the number of subjects completing Visit 3.

To assess the robustness of the conclusion based on observed data for the primary endpoint, sensitivity analyses imputing missing data is proposed as the following:

1. Worst-case analysis: All subjects not completing Visit 3 will be assumed to have not achieved TE.

2. Best-case analysis: All subjects not completing Visit 3 will be assumed to have achieved TE.

3. Tipping point analysis: All missing data will be imputed with either having achieved TE or not achieved TE, i.e., the denominator of the TE rate is based on the analysis set. By adding one TE event at each time, the p-value is calculated (worst-case to best-case). The tipping point is when the p-value is changed from (>=0.05 to <0.05). After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point (essentially, if we have 145 ITT patients, tipping point is 126 TE events; if we have 130 ITT patients, tipping point is 113 TE events).

8.8.2 Secondary Endpoints and associated hypotheses

Technical Success and Local Tumor Progression:

Technical Success is defined as: All A0 and A1 ablation classification determinations (complete tumor ablation with a surrounding minimal margin) as assessed by cone beam CT (CBCT) imaging, immediately following the ablation procedure. (Note: A0 = Complete tumor ablation with an ideal minimal margin, i.e., a surrounding minimal margin of at least 5mm. A1 = Complete tumor ablation with a minimal margin, i.e., a surrounding minimal margin of less than 5mm but more than 0mm.)

Local Tumor Progression (LTP) is defined as: Recurrence of originally ablated target tumor(s) within or abutting the ablation zone using 30-day post-ablation imaging as the baseline.

The number and percentage of target tumors achieving Technical Success will be summarized. Local Tumor Progression (target tumors only) will be summarized in a similar manner.

Data collected on non-target tumors for these endpoints will be summarized separately. In addition, Technique Efficacy, Technical Success, and Local Tumor Progression results will be include a subject level summary in addition to the tumor level analysis.

Detail regarding new or recurrent lung tumors post procedure will be summarized similarly to the pre-ablation, such as target/non-target, location, size, and distance from pleura.

Time to Event Endpoints:
Local Tumor Progression Free Survival (LTPFS) is defined as: Time from the ablation until local tumor(s) progression (LTP) or death, whichever occurs first.

Progression Free Survival (PFS) is defined as: Time from the original ablation until tumor(s) progression or death, whichever occurs first (includes local, regional, or distant progression). Specifically: For local tumors, time from the original ablation until tumor(s) progression or death, whichever occurs first. For regional and distant tumors, time from study day 0 or last local therapy (if treated after study initiation) until tumor(s) progression or death, whichever occurs first.

Disease (cancer) Specific Survival (DSS) is defined as: Time from the original ablation until death from the treated primary malignancy.

Overall Survival (OS) is defined as: Time from the original ablation until subject death (includes death from any cause).

Local Tumor Progression Free Survival (LTPFS), Progression Free Survival (PFS), Disease Specific Survival (DSS), and Overall Survival (OS) will be estimated using the Kaplan-Meier method with 95% confidence intervals provided at month 12. The time from the day of the initiation ablation procedure to the specific event will be derived.

Patients who are re-ablated are considered as reaching an event respectively for each of the LTP, LTPFS and PFS event definitions.

Patients without a progression event, as defined above, will be censored by the last contact date (the last date in the study).

Other Secondary Endpoints:

Navigational Success is defined as: Successful navigation to the targeted peripheral lung tumor(s) as confirmed using CBCT.

Repeat Ablation Efficacy Rate is defined as: Rate of original tumors that have been re-ablated successfully (i.e., Technical Success of tumors that have been re-ablated/all original tumors that have been re-ablated).

Change in all available pulmonary function tests (PFTs) is defined as from pre-ablation baseline values to values at 3 months, 6 months, and 12 months post-ablation.

Change in overall health-related quality of life (HRQOL) and subscales, including physical functioning and pain domains, per the validated EORTC QLQ-C30 and QLQ-LC13 questionnaires throughout the duration of the study.

Categorical variables will be summarized with counts and percentages. These include Navigational Success, and Repeat Ablation Efficacy.

Change in all available PFTs (pulmonary function tests) from pre-ablation baseline values to values at 3 months, 6 months, and 12 months post-ablation, change in overall health-related quality of life (HRQOL) and subscales (including physical functioning and pain domains) per the validated EORTC QLQ-C30 and QLQ-LC13 questionnaires throughout the duration of the study will be summarized descriptively with n, mean, SD, min, max, Q1, and Q3.

Re-ablation or subsequent treatment may impact the quality of life and/or pulmonary function. Hence, a separate summary may be presented for PFT, HRQOL by excluding those patients who have re-ablation, or received other treatment during the study.

8.9 Exploratory Endpoints

Level of Procedure Related Pain: Subject reported outcome determined by the Numeric Pain Scale.

Subject functionality as measured by distribution of Eastern Cooperative Oncology Group (ECOG) classification scores over time.

Hospital Readmission Rate: Any unplanned admission or readmission to the hospital within 30 days of the ablation procedure due to an adverse event.

Procedural cost (UB-04) for US sites.

Number of systemic chemotherapy-free days from time of ablation through the duration of the study.

Number of systemic chemotherapy-free days will be summarized separately for those subjects without any plans for systemic therapy post local therapy and for subjects with plans for post ablation/SBRT/surgery systemic therapy.

Categorical variables will be summarized with counts and percentages. These include hospital readmission (unplanned admission or readmission within 30 days of ablation due to an AE) and ECOG. Re-ablation or subsequent treatment may impact the ECOG results. Hence, a separate summary may be presented for ECOG excluding those patients who have re-ablation, or received other treatment during the study.

Level of Procedure Related Pain (0 to 10), procedural cost from UB-04 form, if available, and number of systemic chemotherapy-free days (from time of ablation through the duration of the study) will be summarized descriptively with n, mean, SD, min, max, Q1, and Q3.

8.10 Central Review v. Investigator on Effectiveness Analysis

The effectiveness-based endpoints will be evaluated both by the treating physician (i.e., PI) as well as the independent Central Review Committee. Both sets of results will be summarized in the final report, with the Central Review Committee results being specified as the primary result for Technique Efficacy, Technical Success, Local Tumor Progression, Other Progression (regional and distant), the smallest/largest ablation zone, and the smallest margin.

8.11 Safety Analyses

Perioperative AEs are defined as AEs that occur from the time of subject consent through 30-days post any ablation procedure (i.e., the original ablation as well as any re-ablation) regardless of relationship to the study device or procedure.

Device-/procedure- related AEs are defined as AEs that are deemed related to the study device or procedure 30-days post any ablation procedure (i.e., the original ablation as well as any re-ablation) through the end of the study or early discontinuation.

Serious adverse events (SAEs) will be captured from the time of subject consent through the end of the study or early discontinuation regardless of relationship to the study device or procedure.

The number and percentage of subjects experiencing perioperative AEs, device- and procedure-related AEs, and all SAEs will be summarized by MedDRA system organ class and preferred term. A similar summary will also be provided for all SAEs from Visit 3 (the first post-ablation visit) through Visit 6 (end of study) as well as for the entirety of the study (Visit 1 – Visit 6).

Ninety-five percent confidence intervals may be provided for pre-specified adverse events of interest, which are:

1. Pneumothorax (overall and CTCAE grade ≥ 2)
2. Hemorrhage, bleeding requiring medical intervention (CTCAE grade ≥ 2)
3. Chest wall pain
4. Pleural effusion or emphysema (overall and requiring chest tube drainage)
5. Pneumonia
6. Pulmonary abscess
7. Other lower-tract respiratory infection
8. Bronchopleural fistula.

8.12 Plans for Interim Analysis

There are no plans for any formal interim analyses with intent to stop the study early or to modify the study design. However, non-formal interim analyses are planned. The first interim analysis will occur after 20 subjects complete Visit 3 (30 days) and will be descriptive in nature only and will not impact the final analysis. The second interim analysis will occur after all subjects complete Visit 3 (30 days) and will include an evaluation of the primary endpoint against the performance goal as well as provide a summary of all baseline and procedural-related data. A complete summary of all safety-related data observed through the duration of follow-up on all subjects will also be provided. The intent of this analysis will be to support regulatory filing activities where appropriate.

An additional interim analysis may be performed after all subjects have completed Visit 5 (6 months). The final analysis will be completed once all subjects have completed Visit 6 (12 months) and will summarize all endpoints collected during the trial.

8.13 Handling of Missing Data

No imputation will be used for missing data or early dropouts in all analysis except in the sensitivity analyses for the primary endpoint (see Section 8.8.1). Time-to-event analyses will use standard censoring assumptions for the handling of subjects who do not have event or do not complete follow-up visits (see Section 8.8.2).

8.14 Subgroup Analysis

At a minimum, subgroup analyses are planned to be performed by original histology (sarcoma, renal, colorectal) and tumor size (≤1cm, 1-2cm).

Additional subgroups may be identified pending the distribution of baseline demographic (such as by countries) or clinical characteristics. All subgroup analyses will be descriptive in nature and summary statistics will be provided for procedure-related parameters, time-to-event endpoints, and adverse events.

9 Data Safety Monitoring Board (DSMB)

An independent data and safety monitoring board (DSMB) will be commissioned to review, on a regular basis, safety data from the study. The DSMB will advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited to the study. The initial DSMB review of safety data will be conducted after five subjects have been ablated and completed the 30-day follow-up visit. Additional DSMB reviews will occur after 10 and 20 subjects have been ablated and completed the 30-day follow-up visit. After the review of the initial 20 subjects, the DSMB will determine the appropriate continued frequency for their reviews, which will continue for the duration of the study. Based on accumulating safety data from the study, the DSMB may recommend whether to continue, suspend, modify, or stop the study.

At the conclusion of the review of all enrolled and ablated subjects, the DSMB will also give a final assessment of the safety of the procedure. The composition, responsibilities, frequency of DSMB meetings, handling of emergency situations, and documentation of DSMB meetings is specified in the DSMB Charter.

Additionally, the DSMB will review all reported deaths. A report of death or severe hemorrhage requiring intervention beyond local therapy (i.e., Nashville ≥ grade 2 or CTCAE ≥ grade 2) within 30 days of the procedure will put enrollment on hold and require review by the DSMB to determine if the death or hemorrhage was related to the ablation procedure. The DSMB will determine whether the study may resume enrollment or state other necessary conditions or recommendations to resume enrollment.