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

Protocol Number: NEU_2020_03

Document	**Effective Date**
Version 2.0	18 August 2022

Sponsor:

NeuWave Medical, Inc.
[redacted]

NeuWave Medical, Inc. is a subsidiary of:

Ethicon, Inc.
1000 US Highway 202 South
Raritan, NJ 08869

Name of Finished Product(s):

NEUWAVE™ FLEX MC Microwave Ablation System and Accessories

Sub-products:

NEUWAVE™ FLEX Microwave Ablation System and Accessories

Auris MONARCH® Platform

CONFIDENTIALITY STATEMENT

Johnson & Johnson MEDICAL DEVICES

Sponsor Signature

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INVESTIGATOR SIGNATURE

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practice (GCP), applicable country regulations, the Declaration of Helsinki, the signed clinical study contract with Sponsor, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments and will accept respective revisions or amendments provided by the Sponsor.

_____	_____
Principal Investigator Signature	**Date**
[Principal Investigator printed name]	
[Name of the site / Site MDEV number]	
[Address of the site]	
[City, State, Zip]	
[Country]	

PLEASE RETAIN A SIGNED COPY FOR YOUR STUDY RECORDS

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1.0 PROTOCOL SUMMARY

Full Title	A Prospective Multicenter Study of Transbronchial Microwave Ablation Using Robotic-Assisted Bronchoscopy in Subjects with Oligometastatic Tumors in the Lung	
Protocol Number	NEU_2020_03	
Short Title	POWER Study (Prospective Transbronchial Microwave + Robotic-Assisted Bronchoscopy)	
IDE Number	G210303	
Sponsor	NeuWave Medical, Inc.	
Study Objective	The primary objective of the study is to evaluate the safety and effectiveness of the NEUWAVE™ FLEX MC Microwave Ablation System and Accessories used in transbronchial ablation procedures for adult subjects with oligometastatic tumors (≤ 2cm) in the lung.	
Study Devices	NEUWAVE™ FLEX MC Microwave Ablation System and Accessories Sub-products: • NEUWAVE™ FLEX Microwave Ablation System and Accessories • Auris MONARCH® Platform	
Study Design	Prospective, multicenter, single-arm study	
Study Population	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 histologies.	
Potential Geographic Areas to be Included	United States, Hong Kong, Canada, and China	
Anticipated Study Timelines	Enrollment: 2 years	Follow-Up: 1 year
Sample Size	Up to 145 subjects ablated	
Procedure Description	Transbronchial microwave ablation will be performed using the NEUWAVE™ FLEX Microwave Ablation System and Accessories on oligometastatic tumors in the peripheral lung, guided by the Auris MONARCH® Platform for visualization and access while using cone	

	beam CT (computed tomography) to confirm probe tip placement and final ablation zone.
Primary Endpoint	Technique Efficacy: 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.
Safety Endpoint	Adverse events (AEs) will be assessed from the time of subject consent. • Perioperative AEs will be captured 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. • AEs that are deemed related to the study device or procedure will be captured 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.
Secondary Endpoints	• Technical Success: All A0 and A1 ablation classification determinations (complete tumor ablation with a surrounding minimal margin) as assessed by cone beam CT imaging, immediately following the ablation procedure. • Navigational Success: Successful navigation to the targeted peripheral lung tumor(s) as confirmed using cone beam CT (CBCT). • Local Tumor Progression (LTP): Recurrence of originally ablated target tumor(s) within or abutting the ablation zone using 30-day post-ablation imaging as the baseline. • Local Tumor Progression Free Survival (LTPFS): Time from the ablation until local tumor(s) progression (LTP) or death, whichever occurs first. • Progression Free Survival: Time from the original ablation until tumor(s) progression or death, whichever occurs first (includes local, regional, or distant progression). • Disease (cancer) Specific Survival: Time from the original ablation until death from the treated primary malignancy. • Overall Survival: Time from the original ablation until subject

	death (includes death from any cause). • Repeat Ablation Efficacy Rate: 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 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 sub-scales, including physical functioning and pain domains, per the validated EORTC QLQ-C30 and QLQ-LC13 questionnaires throughout the duration of the study.
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 re-admission to the hospital within 30 days of the ablation procedure due to an adverse event. • Procedural cost (UB-04). • Number of systemic chemotherapy-free days from time of ablation through the duration of the study.
Inclusion Criteria	1. Signed informed consent. 2. Subjects ≥ 22 years old. 3. Performance status 0-2 (Eastern Cooperative Oncology Group classification [ECOG]). 4. Willing to fulfill all follow-up visit requirements. 5. Subjects with no more than five oligometastatic tumors in no more than three organ sites with no more than three tumors in any single organ. 6. Presence of at least one oligometastatic lung tumor with colorectal, renal, or sarcoma histology where the primary tumor is controlled (in the opinion of the investigator or treating oncologist). Histology should be documented by the following criteria: 1) biopsy of target lesion, if feasible, **or** 2) imaging highly suspicious for metastatic lesion in context of a previous biopsy of the primary or other metastases. 7. Oligometastatic lung tumor(s) planned to be ablated should be ≤ 2cm (based on the Screening Visit image), in the outer two-thirds of the lung, and not closer than 1cm to the pleura

	(including fissures) or contiguous with the pleura. The outer two-thirds is defined as beyond the segmental airway, such that proximal endobronchial soft tissue tumors are avoided.
Exclusion Criteria	1. Pregnant or breastfeeding. 2. Subjects with thoracic implantable devices, including pacemakers or other electronic implants. 3. Chronic, continuous ventilator support, which uses bi-level positive airway pressure (PAP) to improve lung function for severe conditions. (However, intermittent PAP, for non-pulmonary conditions, such as sleep apnea, is permitted). 4. Prior pneumonectomy. 5. Severe bronchiectasis (with FEV1 <30%) or disease deemed to be too severe in the opinion of the investigator. 6. Clinical or imaging findings consistent with an active pulmonary infection. 7. Platelet count ≤ 50,000/mm^3. 8. Subjects with uncorrectable coagulopathy at time of screening. 9. Subjects medically unable to stop anti-platelet agents (e.g., aspirin, clopidogrel, prasugrel, ticagrelor) at least **5 days** prior to the procedure through 48-72 hours after the procedure. 10. Subjects medically unable to stop warfarin at least **3-5 days** prior to the ablation procedure, or until INR ≤ 1.5, through 48-72 hours after the procedure. On the day of the procedure, subjects with an INR > 1.5 cannot have the procedure completed that day but may be rescheduled or postponed. 11. Subjects medically unable to stop anticoagulants (e.g., rivaroxaban, apixaban, dabigatran, endoxaban) at least **3 days** prior to the ablation procedure through 48-72 hours after the procedure. 12. Subjects who require heparin or low molecular weight heparin bridging. 13. Expected survival less than 6 months, in the opinion of the investigator and/or treating oncologist. 14. Subjects with known or suspected brain metastases. 15. Subject has had any radiation (i.e., SBRT or EBRT) to the intended ablation zone. 16. Endobronchial tumors proximal to and including the segmental airways. 17. Tumors where the anticipated zone of ablation would encompass significant (in the opinion of the treating physician) emphysematous or bullous disease. 18. Subject who underwent lung ablation, surgical resection therapy, radiotherapy, or any other treating procedure within 30 days prior to the planned study ablation procedure or those who plan to receive a lung ablation, surgical resection, or

	radiation therapy on the ablated lung side before completing the primary endpoint assessment (30 days post-ablation). 19. Subject who received systemic therapy (e.g., chemotherapy, targeted drug therapy, or immunotherapy) within 14 days prior to the planned study ablation procedure or those who plan to receive systemic therapy before completing the primary endpoint assessment (30 days post-ablation). 20. Uncontrolled hypertension pre-procedure (Visit 2). Defined as systolic blood pressure ≥ 160mmHg and/or diastolic blood pressure ≥ 100mmHg despite pharmacotherapy. 21. Subjects who have participated in an investigational drug or device research study within 30 days of enrollment that would interfere with the primary endpoint of this study. 22. Physical or psychological condition that would impair study participation. 23. Severe neuromuscular disease. 24. Subjects judged unsuitable for study participation by the Investigator for any other reason. Intra-operative exclusion criteria that lead to stopping a procedure: 25. Inability to tolerate anesthesia. 26. Time of navigation to initiation of ablation longer than 60 minutes, per target tumor. 27. Bleeding estimated to exceed 50cc (visualization via the drainage system) or a Nashville grade 2 or higher intervention is required (see Appendix 2). 28. If the CBCT imaging after a bleeding episode obscures the radiographic visibility of the tumor such that the ablation probe/tumor relationship is not discernable, the procedure should be terminated. 29. Any presenting condition discovered intra-procedurally that in the opinion of the Investigator would make participating in this study not in the subject's best interest.
DSMB (Data Safety Monitoring Board)	An independent Data Safety Monitoring Board (DSMB) will be commissioned to periodically review safety events from the study to ensure safety trends are consistent with the current safety profiles of the devices. Specifically, 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 an ablation procedure will temporarily stop enrollment and require review by the DSMB.
Statistical Analyses	The number and percentage of tumors achieving Technique Efficacy will be summarized and a confidence interval will be estimated.

	Technical Success, Repeat Ablation Efficacy, and Hospital Readmission Rate will be summarized in a similar manner. Local Tumor Progression, Local Tumor Progression Free Survival, Progression Free Survival, and Overall Survival will be estimated using the Kaplan-Meier method and confidence intervals will be provided. The number and percentage of subjects experiencing device-related AEs will be summarized by the MedDRA system organ class and preferred term. A similar summary will also be provided for procedure-related AEs and all SAEs. Summary statistics will be provided for all other endpoints as defined within the protocol.
Interim Analyses	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.
Time and Events Schedule	See Table 1 on the next page.

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							

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									
Chest CT[10]	X[11]				X[12]	X	X	X	
Abdomen and Pelvis CT[10]	X[13]					X	X	X	
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				

Table 1 Notes:

1. Medical history, radiation history, surgical history, and smoking status.
2. Record all relevant prior medications (taken within 30 days of Visit 2) and all relevant concomitant medications taken throughout the study, including but not limited to blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events. Do not record components of the anesthesia medications used for the ablation procedure. Prophylactic antibiotics should be administered pre-ablation per site standard-of-care (SOC).
3. Key vitals include: blood pressure, heart rate, and pulse oximetry.

4. Only for women of childbearing potential. Tested per site SOC (urine or serum) if/when applicable.
5. Coagulation tests, including APTT and PT/INR, per site SOC.
6. INR should be one of the first assessments completed on the ablation day to ensure it is ≤ 1.5 or the ablation should be rescheduled. Other assessments, if completed, do not need to be repeated as long as the ablation is completed within two weeks of the originally scheduled ablation.
7. Data for any serum-based tumor markers (e.g., CEA and LDH) or molecular profiling, if completed as part of SOC.
8. Quality of Life questionnaires include the validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed, using the Sponsor-provided script.
9. Ablation procedure details include, but are not limited to, the following: date and time of procedure, anatomical location of ablations, number of ablation cycles, time and power used for each ablation, number of cone beam CT scans performed for probe placement and margin assessment, number of probe placement attempts per ablation, type of probe(s) used, type of anesthesia, duration of procedure (the time when the bronchoscope enters the endotracheal tube to the time when the last cone beam CT scan is taken) and radiation exposure from CBCT scans and the entire procedure.
10. Contrast-enhanced is preferred for these CT images (chest, abdomen, and pelvis), but not required.
11. CT scan of the chest is used at Screening to determine tumor details (e.g., size, location, and type, if available). Tumor size must be measured in 3 axes (axial, sagittal, and coronal).
12. CT scan of the chest is used at every follow-up visit to determine tumor details (e.g., size and location) and to assess local tumor control. If PET (positron emission tomography) scan is taken during follow-up as part of SOC, the site must also perform the diagnostic CT as per protocol. Technique Efficacy and Local Tumor Progression will be determined based on image analysis.
13. The abdomen and pelvis CT required at Screening does not have to be repeated if a previous abdomen and pelvis CT was complete d within 90 days of the visit.
14. Brain MRI (with or without contrast) is preferred to be completed at requested timepoints (Screening and Visits 4, 5, and 6), but is not required, and should be taken per site SOC. A brain MRI may be included as part of the Screening imaging if it was completed within 12 months of the visit.
15. For patients with an extremity sarcoma, extremity CT or MRI (with or without contrast) is preferred to be completed at requested timepoints (Screening and Visits 4, 5, and 6), but is not required, and should be taken per site SOC. An extremity CT or MRI may be included as part of the Screening imaging if it was completed within 90 days of the visit.
16. Measure and record the size of the tumor(s) on the day of ablation using CBCT. Afterwards, use cone beam CT to guide the microwave ablation probe to the target tumor(s) and ascertain the location of the probe after the robotic bronchoscope has been retracted. CBCT scans will be used at a minimum of three timepoints pre- and post- the ablation process: (1) Pre-Navigation: Prior to starting navigation, CBCT will be used to establish baseline imaging, confirm tumor details, and tumor segmentation for navigation (i.e., augmented fluoroscopy), (2) Pre-Ablation: Immediately before the ablation, use CBCT to confirm that the probe is in the intended location, and if it is not, reposition the probe, and (3) Post-Ablation: After completing the ablation, use CBCT to confirm that the ablation margins are adequate. Note: Technical Success will be determined based on CBCT image analysis.
17. Perioperative AEs will be captured 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. AEs that are deemed related to the study device or procedure will

be captured 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 termination. 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.

18. UB-04 data collection is applicable for US sites only.
19. Length of hospital stay (LOS), measured from post-ablation to discharge. After the ablation procedure, the subject will be observed for up to 23 hours before discharge, except in cases where the Investigator deems it is necessary for the subject to remain hospitalized.
20. Record readmission to any hospital for any unplanned reason within 30 days of any ablation procedure (i.e., the original ablation as well as any re-ablation). The Investigator will assess the reason for the admission and capture the reason in the clinical database.
21. Record reason for unscheduled visit, as well as AEs (if applicable), and any updates to concomitant medications, concomitant procedures, or any other study assessments, per site SOC.

2.0 ETHICS

Institutional Review Board/Ethics Committee

Participating investigators will ensure that this protocol, Informed Consent Form (ICF), and if applicable, any protocol amendments or other written information provided to the subjects who assist in the decision to participate are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical investigation. Participating investigators will be required to promptly report new protocol amendments and new ICFs to the IRB/EC as required by the IRB/EC's policies. Additionally, investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to study subjects or others.

Applicable Regulations

This study will be conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki, as well as any other applicable local and country regulatory requirements.

Subject Information and Consent

Regulations concerning the protection of subjects require that informed consent be obtained before a subject may participate in any clinical investigation. Screening assessments that are part of standard-of-care (SOC) may occur prior to consent; however, the data may not be collected for study purposes until the ICF has been signed by the subject.

An IRB/EC approved informed consent must be sought from each subject and must be appropriately documented in the subject's medical record prior to initiating the study. It is the Investigator's responsibility to obtain written informed consent from the subject, however, the Investigator may delegate this responsibility if appropriately documented.

The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate time for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's written consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICF is presented in native, non-technical language that is understandable to the subject.

Prior to a subject's participation in this study, an ICF will be signed and dated by the subject and person who conducted the consent discussion. The subject will be provided a copy of the signed ICF. The ICF and any other written materials provided to the subject to assist in the decision to participate must be revised whenever new information becomes available that may be relevant to their willingness to participate or continue participation in this study. Revision to the ICF and other written materials will receive IRB/EC approval before implementation. Each subject will be required to sign any amended ICF (as required by the IRB/EC) and will receive a copy of the signed ICF.

Administrative Requirements

This study is sponsored by NeuWave Medical, Inc. and will be conducted under a single protocol approved by each participating site's IRB/EC prior to implementation. The principal investigator must be either an interventional pulmonologist or thoracic surgeon qualified by education, experience, and training to perform the study procedure and to assume responsibility for the conduct of this study.

The Data Management and Biostatistics groups of NeuWave Medical, Inc. will be responsible for the analysis of data from this protocol. An electronic data capture (EDC) system will be utilized by study site personnel to transfer study data from source records (the first point of clinical data capture) onto common electronic case report forms (eCRFs). This system is a web-based, secure electronic software application [redacted] This system was designed and is developed and maintained by [redacted] in a manner that is compliant with national and international Good Clinical Practice (GCP) data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements.

Protocol Modifications

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/EC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number). The Investigator reports the protocol amendments to the site's IRB/EC as per their local requirements.

3.0 INTRODUCTION

Oligometastatic lung tumors & rationale for local control

A subset of subjects with metastatic malignancy will present with a limited number of metastases and a low burden of disease. This intermediate state between localized cancer and widely metastatic disease – so-called oligometastatic disease state – occurs in a variety of primary tumor types, with colorectal carcinoma, renal cell carcinoma, and soft tissue sarcoma being the most common.[1] Oligometastatic disease is most commonly defined as having up to five sites of metastasis from a primary tumor with a maximum of three metastases in any one organ.[2] The lungs are a frequent site of oligometastatic disease.[3,4] While palliative systemic chemotherapy is the standard for subjects with widely metastatic disease, local therapies are the preferred treatment approach for subjects with oligometastatic disease.

The rationale for local therapy in this population is that aggressive treatment (e.g., surgery, SBRT) of the demonstrable sites of disease may result in a prolonged disease-free state. In addition, local therapy may obviate the need for systemic chemotherapy and its associated toxicity. This strategy has traditionally involved surgical resection, with the hope that removing all local sites of disease would result in an improved survival. However, robust clinical evidence to support improvements in survival are lacking. Observational studies in subjects undergoing surgical metastasectomy have noted improved survival, although subject selection bias remains a possible explanation for these findings.[5,6] Another study highlighted the potential benefit of local control by noting a significant improvement in overall survival (OS) between those subjects who achieved a complete resection compared to those where only an incomplete resection was possible (36% OS at 5 years vs. 13% OS at 5 years).[2] On the other hand, the only randomized trial of surgical metastasectomy compared to standard of care therapy in subjects with pulmonary metastases from colorectal carcinoma demonstrated no survival benefit.[7] Nonetheless, these studies have led to the increased adoption and acceptance of local therapy as the preferred treatment strategy in subjects with a limited number of metastatic lesions.

Survival outcomes do not vary by modality used to achieve local control

Although local control of metastases has generally been accomplished with surgical resection, many subjects are not candidates for surgery, and non-surgical approaches to local therapy are increasingly employed. In the lung, stereotactic body radiation therapy (SBRT) and image-guided thermal ablation (IGTA) are currently available. Similar to surgical metastasectomy, studies suggest/show there is no evidence of a survival benefit across these non-surgical treatment modalities. The Sponsor's ongoing systematic review and meta-analysis examining outcomes in subjects with pulmonary metastases treated with SBRT or IGTA has identified a total of 21 studies [restricted to studies with at least 40 subjects]. The 1-year progression free survival (PFS) rate of these options was found to be similar; 58% (95% CI:49%-67%) for IGTA and 60% (95%CI:52%-67%) for SBRT. Published literature has also demonstrated similarity in survival outcomes between these approaches: a published meta-analysis demonstrated similar outcomes for IGTA and SBRT with 3 years OS around 45-65% for these options.[8] These results are similar to the outcomes seen in surgical series, with reported 3 years overall survival of 40-60%.[9,10] As a result, several clinical guidelines have suggested that surgical resection, ablation, or SBRT may all be considered for local treatment of pulmonary metastases.[11,12]

Transthoracic ablation as a treatment modality in oligometastatic subjects

Given the lack of data supporting a survival advantage of one therapeutic modality over another, the benefit-risk profile of all available options must be considered. The clinical decision to pursue one therapeutic modality over another is complex and dependent on lesion location, size, underlying comorbidities, pulmonary function, estimated success at achieving local tumor control, anticipated short- and long-term adverse events, and impact on physical functioning, pain, and health-related quality of life. As a result, shared decision making and subject preference become critical factors in the clinical decision. Several studies have demonstrated that subjects with metastatic malignancy prefer therapies that minimize the impacts on their health-related quality of life (e.g., pain, adverse events, functioning) and which may preclude the need for systemic chemotherapy.[13,14,15] Percutaneous ablation is a minimally invasive, out-patient procedure that has demonstrated efficacy in the treatment of pulmonary metastases, with high rates of complete tumor ablation (>90%) and subsequent local tumor control (>85%).[16] In addition, subjects treated with percutaneous ablation experience minimal impact on health-related quality of life, particularly as it pertains to physical functioning, role functioning, pain, and fatigue.[17,18,19] As a result, percutaneous ablation is increasingly used in the treatment of pulmonary oligometastatic disease and there is equipoise in the clinical guidelines between surgery, SBRT and IGTA.[11,20,21]

Transbronchial microwave ablation (MWA)

While radiofrequency ablation (RFA) was historically the most commonly used ablative modality for percutaneous lung ablation, microwave ablation (MWA) is now the preferred option. This is largely due to MWA's ability to create larger, more uniform ablation zones in a shorter period of time as a result of MWA's improved ability to propagate through and heat high impedance lung tissue and less susceptibility to vascular "heat sinks".[22] While the percutaneous approach to MWA has been more widely adopted, the transbronchial approach offers potential advantages including a lower risk of pneumothorax, bleeding, and other pleural based complications such as pleural effusion, empyema, and bronchopleural fistula. A few pilot studies have tested the feasibility of this approach.[23] The largest of these reports included 25 subjects with mixed primary non-small cell lung cancer (NSCLC) and oligometastatic lesions to the lung who were considered poor surgical candidates or opted out of surgery.[24] In this single center retrospective experience, 30 lesions (≤ 3cm) in 25 subjects were treated. Pneumothorax requiring a chest tube was reported in 2 subjects (6.7%), Grade 1 hemoptysis and an infected pleural effusion in 1 subject each. One death was reported at 12 months deemed unrelated to the procedure. During a median follow up of 1 year, no progressive disease was identified.

The Sponsor has also conducted a prospective pilot study using the NEUWAVE™ FLEX Microwave Ablation System and flexible probes in combination with electromagnetic navigational bronchoscopy (NCT03603652).[23] This study enrolled 10 subjects with primary NSCLC who either refused surgery or were deemed to be poor surgical candidates. Subjects underwent image guided ablation of their target lesion (≤ 2cm). The primary endpoint of technique efficacy was judged by the treating physician to have been achieved in all cases, and over 1 year of follow up, 1 subject was deemed to have had a recurrence of their disease. No pneumothoraces were reported in this study. Two subjects died during the study, 1 of which was periprocedural and was deemed to be probably related to the procedure. In this case, navigation to the lesion was prolonged and bleeding was observed during the navigation. The subject died 2 weeks later of a presumed pulmonary hemorrhage though no autopsy was performed. While the DSMB stated the study could continue

with protocol modifications, the Sponsor stopped the study to update the study design based on feedback from the DSMB and FDA and to re-start the study under an Investigational Device Exemption (IDE) protocol.

Robotic Assisted Transbronchial Ablation:

The Sponsor has since combined the precision of robotic-assisted bronchoscopy (RAB) with the efficiency of microwave ablation into a single system called the NEUWAVE™ FLEX MC Microwave Ablation System and Accessories (i.e., "FLEX MC"), which is planned to be used in the current study (see Section 6.2 of protocol). Conceptually, combining the micro-precision and direct visualization of RAB would allow for more precise placement of ablation probe, ideally in the center of the lesion, which could lead to fewer ablations needed to obtain the desired ablation zone. In support of this concept, several studies have noted a higher rate of nodule localization with RAB compared to other peripheral bronchoscopy techniques. The BENEFIT trial evaluating the Monarch platform noted a lesion localization rate of 96%.[25] With traditional bronchoscopy, studies evaluating versions of the electromagnetic navigation using a variety of platforms have noted localization rates ranging from 81.2% to 88.1%.[26,27] This improved precision and accuracy of navigation is likely to lead to reduced procedural times, as the often time-consuming process of probe repositioning prior to ablative therapy should be reduced.

The RAB used in this study will be the MONARCH® Platform [redacted] which is 510K cleared (K211493) in the United States for both diagnostic and therapeutic procedures (i.e., "MONARCH Platform"). The safety of this platform has been studied in a number of clinical studies as well as in the post marketing setting with over 9,500 procedures performed to date.

The MONARCH Platform was first tested in a clinical feasibility study of 15 subjects.[28] In that study, robotic bronchoscopy to access the periphery of the lung was technically feasible, and it resulted in no serious adverse events and no procedure- or device-related complications. An additional clinical study was completed looking at the feasibility of using MONARCH in subjects (n=55) with peripheral pulmonary lesions. Results from this study showed a safety profile of the robotic-assisted bronchoscopy to be comparable with conventional transbronchial biopsy. The robotic platform successfully localized approximately 96% (51/53) of lesions, and pneumothorax was reported in 2/54 (3.7%) of cases, requiring tube thoracostomy in 1/54 (1.9%) case.[25] No additional adverse events were reported. In addition, the Sponsor has an ongoing 1,200 patient prospective, observational study (the TARGET study) to further characterize the diagnostic performance of the MONARCH Platform in transbronchial biopsies of pulmonary nodules (NCT04182815).

The NEUWAVE FLEX Microwave Ablation System (NeuWave Medical, Inc., Madison, WI) will be paired with the MONARCH Platform, and studied under this protocol as "FLEX MC" under an IDE issued by the FDA.

Transbronchial ablation of lung tumors will involve a physician operator using the MONARCH Platform to provide bronchoscopic visualization and access to targeted lung tumors before precisely placing the FLEX probe into the desired anatomical location manually via the working channel (lumen) of the MONARCH bronchoscope. Once the FLEX probe is precisely positioned, the physician operator can then ablate for up to several minutes until the targeted lung tissue is treated. The MONARCH Platform enables precise control and stability of a flexible bronchoscope

under continuous and direct control by a physician operator, while allowing for continuous real-time visualization of targeted lung anatomy throughout the procedure.

[redacted]

[redacted]

Conclusion

FLEX MC has the potential to fill an unmet need as an effective, precise, repeatable, minimally invasive local therapy option that preserves physical function and health-related quality of life in subjects with oligometastatic disease. By leveraging the safety advantages of bronchoscopy relative to percutaneous access with regards to pneumothorax and other pleural based complications, FLEX MC has the potential to offer subjects the benefits seen with transthoracic ablation with an improved risk profile. The proposed study will evaluate the benefit risk profile of FLEX MC in a population of subjects with oligometastatic tumors in the lung.

4.0 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of the study is to evaluate the safety and effectiveness of the NEUWAVE™ FLEX MC Microwave Ablation System and Accessories used in transbronchial ablation procedures for adult subjects with oligometastatic tumors (≤ 2cm) in the lung.

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).

4.1 Primary Endpoint

- Technique Efficacy: 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.

4.2 Safety Endpoint

- Adverse events (AEs) will be assessed from the time of subject consent.
    - Perioperative AEs will be captured 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.
    - AEs that are deemed related to the study device or procedure will be captured 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.

4.3 Secondary Endpoints

- Technical Success: All A0 and A1 ablation classification determinations (complete tumor ablation with a surrounding minimal margin) as assessed by cone beam CT imaging, immediately following the ablation procedure.
- Navigational Success: Successful navigation to the targeted peripheral lung tumor(s) as confirmed using cone beam CT (CBCT).
- Local Tumor Progression (LTP): Recurrence of originally ablated target tumor(s) within or abutting the ablation zone using 30-day post-ablation imaging as the baseline. Measuring progression details will be outlined in a separate Imaging Charter.
- Local Tumor Progression Free Survival (LTPFS): Time from the ablation until local tumor(s) progression (LTP) or death, whichever occurs first. Measuring progression details will be outlined in a separate Imaging Charter.

- Progression Free Survival: Time from the original ablation until tumor(s) progression or death, whichever occurs first (includes local, regional, or distant progression). Measuring progression details will be outlined in a separate Imaging Charter.
- Disease (cancer) Specific Survival: Time from the original ablation until death from the treated primary malignancy.
- Overall Survival: Time from the original ablation until subject death (includes death from any cause).
- Repeat Ablation Efficacy Rate: 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 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 sub-scales, including physical functioning and pain domains, per the validated EORTC QLQ-C30 and QLQ-LC13 questionnaires throughout the duration of the study.

4.4 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 re-admission to the hospital within 30 days of the ablation procedure due to an adverse event.
- Procedural cost (UB-04), applicable for US sites only.
- Number of systemic chemotherapy-free days from time of ablation through the duration of the study.

4.5 Central Review Committee

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 assessment for the following key endpoints will be used for the final analysis. The central review committee will analyze uploaded subject images from the site to assess the following key endpoints and data:

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 composition of the committee and details of how the endpoints will be defined will be specified in a separate Imaging Charter, which will be finalized prior to enrolling the first subject.

4.6 Additional Measurements/Data Collected

- Subject demographics, baseline characteristics (e.g., BMI, pregnancy status, coagulation tests, and CBC with differential), and key vitals.
- Relevant past medical, surgical, and radiation history as well as smoking status.
- Primary disease details (date of biopsy/diagnosis, histology, treatment type and date(s), and confirm that the disease is controlled (i.e., stable disease imaging at the site of the primary tumor for at least three months before participating in this study).
- Serum-based tumor markers (e.g., CEA and LDH) or molecular profiling, if done as part of SOC.
- Oligometastatic tumor(s) details (e.g., number of oligometastatic tumor(s) and location/organ, whether proven by biopsy or via imaging showing tumor(s) to be highly suspicious of metastatic disease, date of biopsy or imaging).
- Target tumor(s) details (size and location). Note: a biopsy is not required for each target tumor, though it is preferred.
- MONARCH navigation procedure details:
    - Distance from the tip of scope to the tumor(s) as measured by the MONARCH navigation software.
    - Navigation time (time to CBCT confirmation): Time the robotic bronchoscope is inserted into the oropharynx until the localization of the targeted tumor(s) is confirmed by CBCT.
- Ablation details:
    - Number of ablations completed.

  - Time, power, and maximum temperature
  - Procedure Time (including ablation): The time the robotic bronchoscope is inserted into the oropharynx until the time the robotic bronchoscope is removed.
- Probe details (type of probe, number used, number of repositions)
- Imaging details (number of 3D acquisitions performed and estimated radiation exposure)

5.0 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan – Description

This is a prospective, multicenter, single-arm study focused on robotically-assisted transbronchial microwave ablation for adult subjects with oligometastatic tumors in the lung.

Principal Investigators across approximately 15 sites (United States, Canada, Hong Kong, and China) 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.

Prospective subjects will be informed about the nature of the research, given the ICF to read, and if the subject understands the content, will be asked to provide consent by signing the ICF. Individuals scheduled for microwave ablation of the lung will be enrolled after providing informed consent and meeting study entry criteria. Subjects will be followed for 12 months following the first ablation procedure for safety and effectiveness outcomes. Enrollment will continue until up to 145 subjects are enrolled and treated. 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.

Subjects with oligometastatic tumors(s) in the lung who meet all inclusion/exclusion criteria will have transbronchial microwave ablation performed using cone beam CT (computed tomography) scan for probe guidance and confirmation.

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.

5.2 Enrollment

Up to 145 subjects will be enrolled and ablated in this clinical study. A subject is considered to be enrolled when the ICF is signed. Enrollment will continue until up to 145 subjects have been enrolled and had the ablation procedure is initiated. Participants who have the navigation initiated but do not receive the microwave ablation will either have the ablation rescheduled, pending cause, or will be considered an intra-operative withdraw/screen fail and will not count toward the 145 subjects enrolled and ablated.

If a subject experiences an adverse event (AE) after navigation and does not receive the microwave ablation, the subject should be followed from a safety perspective until the AE resolves or is deemed stable.

5.3 Inclusion Criteria

Subjects satisfying the following criteria will be eligible to participate in this study:

1. Signed informed consent.
2. Subjects $\geq$ 22 years old.
3. Performance status 0-2 (Eastern Cooperative Oncology Group classification [ECOG]).
4. Willing to fulfill all follow-up visit requirements.

5. Subjects with no more than five oligometastatic tumors in no more than three organ sites with no more than three tumors in any single organ.
6. Presence of at least one oligometastatic lung tumor with colorectal, renal, or sarcoma histology where the primary tumor is controlled (in the opinion of the investigator or treating oncologist). Histology should be documented by the following criteria: 1) biopsy of target lesion, if feasible, **or** 2) imaging highly suspicious for metastatic lesion in context of a previous biopsy of the primary or other metastases.
7. Oligometastatic lung tumor(s) planned to be ablated should be ≤ 2cm (based on the Screening Visit image), in the outer two-thirds of the lung, and not closer than 1cm to the pleura (including fissures) or contiguous with the pleura. The outer two-thirds is defined as beyond the segmental airway, such that proximal endobronchial soft tissue tumors are avoided.

Note 1: A maximum of two ipsilateral oligometastatic tumors may be ablated during a single session as part of this protocol. The tumor size measurement will be based on the Screening Visit image and does not need to be re-confirmed on the Ablation Day.

Note 2: A maximum of three total oligometastatic lung tumors may be ablated as part of the protocol during the entire study follow-up period.

Note 3: A second or third oligometastatic lung tumor may only be ablated if its planned ablation zone does not overlap with the ablation zone of the previously ablated tumor(s).

5.4 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in this study:

1. Pregnant or breastfeeding.
2. Subjects with thoracic implantable devices, including pacemakers or other electronic implants.
3. Chronic, continuous ventilator support, which uses bi-level positive airway pressure (PAP) to improve lung function for severe conditions. (However, intermittent PAP, for non-pulmonary conditions, such as sleep apnea, is permitted).
4. Prior pneumonectomy.
5. Severe bronchiectasis (with FEV1 <30%) or disease deemed to be too severe in the opinion of the investigator.
6. Clinical or imaging findings consistent with an active pulmonary infection.
7. Platelet count ≤ 50,000/mm^3.
8. Subjects with uncorrectable coagulopathy at time of screening.
9. Subjects medically unable to stop anti-platelet agents (e.g., aspirin, clopidogrel, prasugrel, ticagrelor) at least **5 days** prior to the procedure through 48-72 hours after the procedure.
10. Subjects medically unable to stop warfarin at least **3-5 days** prior to the ablation procedure, or until INR ≤ 1.5, through 48-72 hours after the procedure. On the day of the procedure, subjects with an INR > 1.5 cannot have the procedure completed that day but may be rescheduled or postponed.

11. Subjects medically unable to stop anticoagulants (e.g., rivaroxaban, apixaban, dabigatran, endoxaban) at least **3 days** prior to the ablation procedure through 48-72 hours after the procedure.
12. Subjects who require heparin or low molecular weight heparin bridging.
13. Expected survival less than 6 months in the opinion of the investigator and/or treating oncologist.
14. Subjects with known or suspected brain metastases.
15. Subject has had any radiation (i.e., SBRT or EBRT) to the intended ablation zone.
16. Endobronchial tumors proximal to and including the segmental airways.
17. Tumors where the anticipated zone of ablation would encompass significant (in the opinion of the treating physician) emphysematous or bullous disease.
18. Subject who underwent lung ablation, surgical resection therapy, radiotherapy, or any other treating procedure within 30 days prior to the planned study ablation procedure or those who plan to receive a lung ablation, surgical resection, or radiation therapy on the ablated lung side before completing the primary endpoint assessment (30 days post-ablation).
19. Subject who received systemic therapy (e.g., chemotherapy, targeted drug therapy, or immunotherapy) within 14 days prior to the planned study ablation procedure or those who plan to receive systemic therapy before completing the primary endpoint assessment (30 days post-ablation).
20. Uncontrolled hypertension pre-procedure (Visit 2). Defined as systolic blood pressure ≥ 160mmHg and/or diastolic blood pressure ≥ 100mmHg despite pharmacotherapy.
21. Subjects who have participated in an investigational drug or device research study within 30 days of enrollment that would interfere with the primary endpoint of this study.
22. Physical or psychological condition that would impair study participation.
23. Severe neuromuscular disease.
24. Subjects judged unsuitable for study participation by the Investigator for any other reason.

Intra-operative exclusion criteria that lead to stopping a procedure:

25. Inability to tolerate anesthesia.
26. Time of navigation to initiation of ablation longer than 60 minutes, per target tumor.
27. Bleeding estimated to exceed 50cc (visualization via the drainage system) or a Nashville grade 2 or higher intervention is required (see Appendix 2).
28. If the CBCT imaging after a bleeding episode obscures the radiographic visibility of the tumor such that the ablation probe/tumor relationship is not discernable, the procedure should be terminated.
29. Any presenting condition discovered intra-procedurally that in the opinion of the Investigator would make participating in this study not in the subject's best interest.

Note 1: For Exclusion Criterium 26, the procedure may be attempted again at a later time providing there were no other complications other than an extended navigation time.

Note 2: For Exclusion Criteria 27 and 28, the procedure may be attempted again at a later time, once, in the opinion of the physician, the area of bleeding is fully resolved.

Note 3: For any rescheduled ablations, the ablation should be rescheduled as soon as feasible

but no longer than four weeks after the originally scheduled ablation. Other than INR, other pre-ablation assessments do not need to be repeated.

5.5 Prior and Concomitant Therapy

Subjects may continue with their current medical care throughout the duration of the study, including medications, except as noted in the Exclusion Criteria section of this protocol. All relevant concomitant medications taken within 30 days of Visit 2 and all relevant concomitant medications taken throughout the study, including but not limited to antiplatelet, anticoagulants, chemotherapy, immunotherapies, steroids, anti-inflammatories, NSAIDs, opioids, antibiotics, and medications used to treat adverse events will be recorded on the relevant eCRF page. Components of the anesthesia medication used for the ablation procedure do not need to be recorded on the eCRF page.

In order to avoid confounding the safety and primary effectiveness evaluation, specific treatments/therapies are restricted prior to and after the ablation procedure for given timepoints. The following table summarizes the treatments/therapies restriction timepoints:

Type of Treatment/Therapy	Restriction Prior to Ablation Procedure	Permitted Post Ablation Procedure	Note
Antiplatelet agents (e.g., aspirin, clopidogrel, prasugrel, ticagrelor)	5 days	48-72 hours	Exclusion Criterion #9
Warfarin	3-5 days, or until INR < 1.5	48-72 hours	Exclusion Criterion #10
Anticoagulants (e.g., rivaroxaban, apixaban, dabigatran, endoxaban)	3 days	48-72 hours	Exclusion Criterion #11
Lung ablation, surgical resection, radiotherapy, or other treatment procedure	30 days	30 days (or until Primary Endpoint assessed)	Exclusion Criterion #18
Systemic therapy such as chemotherapy, targeted drug therapy (e.g., tyrosine kinase inhibitors), or immunotherapy (e.g., PD-1 antagonists or CTLA inhibitors)	14 days	30 days (or until Primary Endpoint assessed)	Exclusion Criterion #19

After the restriction timepoint, the above-referenced treatments/therapies may be used at the discretion of the PI and treating oncologist, and should be noted in the eCRFs.

5.6 Screen Failures

All subjects signing consent who do not meet all inclusion and exclusion criteria, or who do not have the procedure initiated (i.e., start of navigation to the target tumor(s)), will be recorded as screen failures. The relevant eCRF pages (Demographics, Inclusion/Exclusion Criteria, AEs, Subject Completion/Discontinuation, etc.) will be completed for all screen failure subjects.

Participants who have the navigation initiated but do not receive the microwave ablation will either have the ablation rescheduled, pending cause, or will be considered an intra-operative withdraw/screen fail and will not count toward the 145 subjects enrolled and ablated.

5.7 Removal of Subjects from the Study

In accordance with the current revision of the Declaration of Helsinki and the Code of Federal Regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw from the study, all efforts will be made to collect any device- or procedure-related AEs or SAEs they may have experienced.

Participation may be terminated prior to completing the study for any of the reasons listed below (reasons that do not fit the categories below will be documented as "other").

Withdrawal of Consent:

If a subject chooses to withdraw early from the study, the eCRF Subject Completion/Discontinuation page should be completed. When a subject's participation is terminated prior to completing the study, the reason for withdrawal is to be documented on the eCRF and in the source documentation.

Investigator Termination:

The Investigator has the right to terminate participation in the study at any time (e.g., for safety or inability to enroll subjects). Should termination of a site be necessary, the Sponsor will provide procedures for termination.

Death:

In the case of subject death, all efforts should be made to get the records documenting the cause of death including postmortem records.

Lost to Follow-Up:

All subjects should be encouraged to return for protocol required clinic visits for evaluation during the study follow-up period. If a subject is unable to return for a clinic visit or unable to be contacted by telephone, attempts to contact the subject should be documented in the source documents. Only after failing to contact the subject at the final follow-up visit, the subject will be considered lost to follow-up and the primary reason for early termination will be completed in the eCRF.

Site Termination or Study Termination:

The Sponsor may terminate a site or the study at any time. When this occurs all subjects at the site will be withdrawn and documented as “early termination.” Reasons for site or study termination may include, but are not limited, to the following:

- Administrative concerns (e.g., inadequate subject enrollment, investigator/institution non-compliance, change of business strategy, etc.).
- Safety issues, including those due to non-compliance, which substantially affect the risk-to-benefit ratio of the study subjects at a site or for the study as a whole.
- Regulatory body mandate(s).

6.0 STUDY PROCEDURES

6.1 Procedure Description(s)

Adult subjects with at least one oligometastatic tumor (≤ 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 will have transbronchial microwave ablation performed using the MONARCH Platform.

Multidisciplinary Team

With regard to the clinical treatment approach for each patient, this is best assessed and determined by a local (i.e., site) multidisciplinary team (MDT) (aka tumor board) directly caring for the subject. An MDT discussion will be required prior to subject ablation to determine or ensure 1) that all oligometastatic tumors present at Screening are deemed treatable, 2) the manner/timing that all disease sites will be treated, and 3) the appropriateness of subject inclusion in the study. The MDT will include, at a minimum, a medical oncologist, thoracic surgeon or appropriate surgical specialist, and radiation oncologist.

Screening and Planning

A CT scan of the lung is used at Screening to determine tumor details (e.g., size, location, and type, if available). Tumor size must be measured in 3 axes (axial, sagittal, and coronal).

A maximum of two ipsilateral tumors that meet all inclusion and exclusion criteria may be ablated during a single session as part of this protocol. The second tumor may only be ablated if its planned ablation zone does not overlap with the ablation zone of the previously ablated tumor.

If a subject had three oligometastatic tumors that met all inclusion and exclusion criteria, but only two could be treated, per protocol, on the “Ablation Visit”, the third, non-target tumor may be ablated at a later study visit. Similarly, if a new, non-target oligometastatic tumor is identified during study follow-up that meets all inclusion and exclusion criteria, it may be ablated. However, only up to three total oligometastatic lung tumors (“target” or “non-target”) may be ablated as part of this protocol during the 12-month follow-up period.

If target tumors recur after the original ablation, they may be re-ablated after the Visit 3 assessment for Technique Efficacy has been completed. A re-ablation will not change or extend the follow-up schedule. Additionally, no single tumor should be ablated more than twice during the 12-month follow-up period (i.e., the original ablation procedure and a re-ablation procedure at a separate visit). **Robotic Navigation Portion of Procedure**

Cone beam CT will be used in all cases to confirm the presence of the tumor(s) immediately before initiating the procedure. Navigation to the target tumor(s) will be performed using the MONARCH Platform. The MONARCH Platform is a novel robotic-assisted, software driven, endoscope articulation system which can electromechanically insert, steer, and withdraw a flexible endoscope to patient airways under continuous, real-time, direct, visual control by a physician operator.

Users must follow all instructions for use supplied with the MONARCH Platform, its components, instruments, and accessories, including any instructions for use (IFUs) provided with instruments or accessories. The provided IFU is the primary source for detailed safety information. The MONARCH Platform and its accessories are intended to provide bronchoscopic visualization of and access to patient airways for diagnostic and therapeutic procedures.

Microwave Ablation Portion of Procedure

The ablation will be performed using the NEUWAVE FLEX MC Microwave Ablation System, per the device's User Manual and Instructions for Use (IFU), and the performing physician's clinical judgment.

All ablations will be performed under general anesthesia via a transbronchial approach. Prophylactic antibiotics should be administered pre-ablation per site SOC.

The size of the tumor(s) will be measured and recorded on the day of ablation (Visit 2). Afterwards, the Monarch Platform will be used to navigate the microwave ablation probe to the target tumor and CBCT will be used to confirm probe position/placement.

If the treating physician believes that bleeding during the navigation or ablation requires intervention, or if the bleeding obscures the view of the tumor or ablation zone, the physician is advised to terminate the procedure. The procedure may be attempted again at a later time, once, in the opinion of the physician, the area of bleeding is fully healed. The ablation should be rescheduled within four weeks of the originally scheduled ablation. Other than INR, other pre-ablation assessments do not need to be repeated.

If the target tumor(s) is within approximately 5mm of a major vessel (in the opinion of the treating physician), this tumor should not ablated, or navigated to, for risk of puncture during the navigation. Additionally, tumors where the anticipated zone of ablation would encompass a significant (in the opinion of the treating physician) emphysematous disease and should also be avoided.

CBCT will be used to guide the microwave ablation probe to the target tumor(s) and ascertain the location of the probe after the robotic bronchoscope has been retracted. CBCT scans will be used at a minimum of three timepoints pre- and post- the ablation process:

(1) Pre-Navigation: Prior to starting navigation, CBCT will be used to establish baseline imaging, confirm tumor details, and tumor segmentation for navigation (i.e., augmented fluoroscopy).

(2) Pre-Ablation: Immediately before the ablation, use CBCT to confirm that the probe is in the intended location, and if it is not, reposition the probe.

(3) Post-Ablation: After completing the ablation, use CBCT to confirm that the ablation margins are adequate.

The smallest and largest length of the entire ablation zone as well as the smallest ablation margin (i.e., distance from the edge of the ablation zone to the edge of the target tumor), must be measured in 3-dimensions and captured in the clinical database.

If a PET scan is taken during the follow-up period, the site must also perform the diagnostic CT as per protocol. PET scans, if obtained, should also be uploaded to the study imaging database with the other required images.

After the ablation procedure, the subject will be observed for up to 23 hours before discharge, except in cases where the Investigator deems it is necessary for the subject to remain hospitalized.

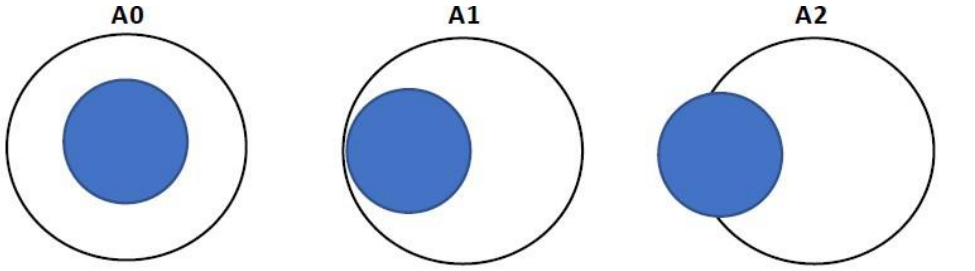
For specific details regarding the microwave ablation procedure and workflow between MONARCH and FLEX, please refer to the User Manual.

Tumor Ablation Classification

Ablation classification used for the determination of Technical Success at the time of the final post-procedure scan for a target tumor will be determined using 3-dimensional (3D) assessment (coronal, sagittal, and axial) and defined as:

- 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).
- A2 = Incomplete tumor ablation.

While Technical Success will be defined as either an A0 or A1 ablation, the goal is to achieve A0 ablation, and this will be a pre-specified secondary analysis. For all A1 and A2 ablation classifications, the PI will document the reason(s) why a margin of at least 5mm was not attainable on the applicable eCRF.



6.2 System Overview

The NEUWAVE FLEX MC Microwave Ablation System is a fully featured soft tissue ablation system that uses small diameter flexible ablation probes, a single high-powered, gas cooled microwave source operating at 2.45 GHz, a CO_2-based cooling system, and a Power Distribution Module (PDM). Microwave energy is applied to the target tissue via a single flexible ablation probe, heating the tissue to the point of necrosis. The FLEX System received 510(k) clearance as a Class II device (K163118) for ablation (coagulation) of soft-tissue.

The FLEX MC Microwave Ablation System is designed to be used in target ablation. Target ablation involves placing a probe into a substantial target and then ablating for up to several minutes until the target tissue is necrotic.

The FLEX probes are designed for improved navigation. They are French gauge 6 (outer diameter of less than 2mm) and 150cm long. The FLEX probes contain three temperature measurement sensors that help monitor performance and ensure subject and operator safety.

The FLEX probe antenna was designed to produce an ablation zone substantially equivalent to the predicate NEUWAVE™ PR probe, but within a flexible probe shaft. Like the predicate PR probe, the FLEX probes were designed to produce ablations that encompass the tip of the probe while limiting the overall length of the ablation. Testing in ex-vivo liver, lung, and kidney tissue confirmed that the FLEX probes produce ablations that are substantially equivalent to the predicate probes.

A CO_2 based cooling system ensures the non-active portion of the probe does not exceed temperature requirements. The system uses two customer-supplied CO_2 cylinders. The system monitors the pressure of the tanks and heats the tanks to maintain the desired tank pressure. The FLEX System will select which cylinder to initially use based upon tank pressures.

The MONARCH Platform enables electro-mechanical articulation and precise control of a flexible bronchoscope under continuous and direct control by a physician operator. The MONARCH Bronchoscope is the subject interfacing component of the MONARCH Platform. Additional components of the platform are the MONARCH Cart and the MONARCH Tower. The Platform received 510(k) clearance as a Class II device (K211493) for diagnostics and therapeutics. The system has several components that interface to the Tower and Cart including: The Fluidics tubing, MONARCH Control, Electro-Magnetic Field generator, and Reference Electro-Magnetic sensors.

The flexible MONARCH bronchoscope has a working channel and a camera at the tip. The camera provides the operative perspective, an integrated light at the scope tip, and a 2.1mm inner diameter working channel for the passing of tools. The bronchoscope's working channel is used for irrigation, aspiration, and access for working channel instruments. The single-use bronchoscope is cleared via K193534, and the equivalent re-processed single-use bronchoscope is cleared via K203614.

The MONARCH Bronchoscope is a comprised of two collinear and concentric devices, the inner scope, and the outer sheath, both of which possess 4-way steering control. This configuration enables the capability of telescoping, which enhances the bronchoscope stability and access capability.

The inner scope and outer sheath have a distal section capable of achieving articulation in pitch, yaw, and any combination of the two to enable precise control while driving the bronchoscope. Proximally, the inner scope is equipped with a valve to facilitate the insertion and sealing of various ancillary devices, such as a biopsy needle or FLEX probes. Additionally, the proximal section routes irrigation and aspiration to the working channel.

6.3 Identity of Study Products

For this study, medical devices will be used in accordance with manufacturer design specifications, product instructions, and guidelines. All study medical devices are described, below:

- NEUWAVE FLEX MC Microwave Ablation System and Accessories

Sub-products of the above device are listed, below:

- NEUWAVE FLEX Microwave Ablation System and Accessories
  - FLEX Microwave Ablation System
  - FLEX Microwave Ablation Probes
- Auris MONARCH Platform
  - Cart
  - Tower
  - Bronchoscope

6.4 Study Product Accountability

The NEUWAVE FLEX MC Microwave Ablation System and Accessories must be stored in conditions according to its labeling and IFU. It is the responsibility of the Principal Investigator (PI) to ensure that devices are stored correctly at their respective site.

The PI, or responsible person designated by the PI, must account for all study devices throughout and, at the end of, the clinical study. During the course of the study, the study's ablation probes must be stored in a locked or secure access location. An inventory record must be maintained of all devices received, used, or returned during the clinical trial. The PI must allow the Study Monitor access to the secured facility where the study devices are stored to check inventory.

The Sponsor may supply the Auris MONARCH Platform (including accessories), the NEUWAVE FLEX Microwave Ablation System, and the microwave ablation probes to the study sites. Upon receipt, the Investigator, or delegated staff, will complete the following:

- Conduct an inventory.
- Upon confirmation that all materials arrived intact, complete the Study Article Accountability Log.
- Retain a copy of the signed and dated Packing List for Clinical Supplies for the Investigator's records.

The study device inventory must be available for periodic inspection/verification by relevant Sponsor representatives, including monitors, auditors, site inspectors (routine or for-cause), any regulatory health authority, or IRB/EC.

7.0 STUDY VISIT SCHEDULE

The Schedule of Assessments may be found in Table 1 at the end of the Protocol Summary.

7.1 Visit 1 – Screening

The screening assessments may occur over several dates within 30 days prior to Visit 2 (Ablation Day), but screening assessments should not be conducted on Visit 2 (Ablation Day).

Subjects will be selected for microwave ablation based on the pre-procedure assessments and the Investigator's interpretation of the clinical picture. Eligible subjects will be provided with the study information, including the ICF.

The following screening assessments will occur prior to the study procedure:

- Subjects must be given ample time to review, ask questions, and sign the ICF.
- PI will review inclusion/exclusion criteria and determine if the subject is eligible to participate in the study.
- Collect demographic information (age at time of Visit 1, sex, race, ethnicity).
- Review and collect medical and surgical history, radiation history, and smoking status.
- Record all relevant prior medications (taken within 30 days of Visit 2), including but not limited to blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events
- Record all concomitant procedures.
- Collect height and body weight for BMI.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.
- Obtain PFTs, which include 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).
- Laboratory tests. If these tests (based on SOC) were completed within 30 days of Visit 2, they do not need to be repeated at the Screening visit:
    - CBC with differentials.
    - Coagulation tests, including APTT and PT per site's SOC. INR is required.
    - Only for women of childbearing potential, complete a pregnancy test per site SOC (urine or serum).
    - Data for any serum-based tumor markers (e.g., CEA and LDH) or molecular profiling on the tumor tissue will be collected, if done as part of site SOC.
- Complete the Numeric Pain Rating Scale.
- Complete two validated quality of life questionnaires: EORTC QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed.
- Chest CT to determine tumor details (e.g., size and location). Tumor size must be measured in 3 axes (axial, sagittal, and coronal). Note: Contrast-enhanced imaging is

preferred, but not required.
- Abdomen and pelvis CT. Note: If the subject had an abdomen and pelvis CT taken within 90 days of the visit, it does not need to be repeated during this visit. Contrast-enhanced imaging is preferred, but not required.
- Brain MRI (with or without contrast), per site SOC. Note: A brain MRI image may be included as part of Screening if it was completed within 12 months of the visit.
- Extremity CT or MRI (with or without contrast), per site SOC. Note: An extremity CT or MRI image may be included as part of Screening if it was completed within 90 days of the visit.
- Record any adverse events (AEs) or serious adverse events (SAEs) that may have occurred after the signing of the ICF.

7.2 Visit 2 – Ablation Procedure Through Discharge

Visit 2: Pre-Procedure

INR should be one of the first assessments completed on the ablation day to ensure it is ≤ 1.5 or the ablation should be rescheduled. Other assessments, if completed, do not need to be repeated as long as the ablation is completed within two weeks of the originally scheduled ablation.

- PI will review inclusion/exclusion criteria and determine if the subject continues to be eligible to participate in the study.
- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.
- Laboratory tests:
  - Coagulation tests, including APTT and PT per site's SOC. INR is required.
  - Only for women of childbearing potential, complete a pregnancy test per site SOC (urine or serum).
- Complete the Numeric Pain Rating Scale.
- Record any AEs or SAEs that may have occurred since the last visit.

Visit 2: Intra-Procedure

The Sponsor will provide access to a Product Development Specialist and/or a Medical Specialist experienced in this procedure for the treating physician as needed. Please refer to the User Manual for additional details.

- CBCT to guide the microwave ablation probe to the target tumor(s) and ascertain the location of the probe after the robotic bronchoscope has been retracted. CBCT scans will be used at a minimum of three timepoints pre- and post- the ablation process:
  (1) Pre-Navigation: Prior to starting navigation, CBCT will be used to confirm general tumor details and tumor segmentation for navigation (i.e., augmented fluoroscopy).
  (2) Pre-Ablation: Immediately before the ablation, use CBCT to confirm that the probe is in the intended location, and if it is not, reposition the probe.
  (3) Post-Ablation: After completing the ablation, use CBCT to confirm that the ablation margins are adequate.
- Perform the microwave ablation procedure: Perform an initial ablation for a maximum of 5 minutes, then after waiting for approximately 10 minutes, perform a CBCT scan to ascertain appropriate progression of the size of the ablation zone. This allows for assessment of the ablation zone to determine whether a sufficient margin has been achieved.
  - If adequate minimal margin was not achieved, additional ablations may be performed.
  - If probe repositioning is required, additional CBCT confirmation is required to ensure the probe is in the intended location.
  - Additional ablations should be no more than 5 minutes per ablation.
  - CBCT imaging must be completed after any additional ablation.
- Record ablation procedure details, including but not limited to:
  - Date and time of the ablation procedure.
  - Anatomical location of ablations.
  - Number of ablation cycles, power, and time used for each ablation.
  - Number of CBCT scans performed for probe placement and margin assessment.
  - Total radiation exposure from the procedure.
  - Number of probes used, type of probes, and probe placement attempts per ablation.
  - Duration of procedure, measured as the time when the bronchoscope enters the endotracheal tube to the time when the last CBCT scan is taken.
- Evaluate Technical Success, defined as all A0 and A1 ablation classification determinations (complete tumor ablation with a surrounding minimal margin) as assessed by **CBCT imaging**, immediately following the ablation procedure.
- Record any AEs or SAEs that may have occurred during the procedure.

Visit 2: Post-Procedure – Discharge

- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events).
- Document any changes or updates to the subject's concomitant procedures.
- Complete the Numeric Pain Rating Scale.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Collect UB-04 data on procedural cost.
- LOS, measured from post-ablation to discharge. Note: after the ablation procedure, the subject will be observed for up to 23 hours before discharge, except in cases where the Investigator deems it is necessary for the subject to remain hospitalized.
- Record any AEs or SAEs that may have occurred after the procedure until the subject is discharged.

7.3 Visit 3 – 30-day Follow-up

Visit 3 occurs 30 days (-7 to +14 days) after the ablation procedure. The subject will visit the study site for the following assessments:

- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Complete two validated quality of life questionnaires: EORTC QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.
- Evaluate Technique Efficacy, defined as 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.
- Record readmission to any hospital for any unplanned reason within 30 days of the ablation. The Investigator will assess the reason for the admission and capture the reason in the clinical database.
- Record any applicable AEs or SAEs:
  - If within 30 days of the ablation procedure, record any AEs or SAEs that may have occurred since the last study visit.
  - If after 30 days of the ablation procedure, record only device- or procedure-related AEs or any SAEs that may have occurred since the last study visit.

7.4 Visit 4 – 3-month Follow-up

Visit 4 occurs 3 months (± 2 weeks) after the ablation procedure. The subject will visit the study site for the following assessments:

- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Complete two validated quality of life questionnaires: EORTC QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.
- Obtain PFTs, which include 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).
- Complete chest CT, abdomen and pelvis CT, brain MRI (if site SOC), and extremity CT or MRI (if site SOC) to determine Tumor Progression. Contrast-enhanced images are preferred but not required. If a site takes a PET scan per SOC, the other images should also be taken, per protocol:
  - Local Tumor Progression (LTP), defined as recurrence of the originally ablated tumor(s) within or abutting the ablation zone using Chest CT and the 30-day post-ablation imaging as the baseline.
  - Regional Tumor Progression includes new or progression of pre-existing tumors that were not previously ablated within either lung using chest CT.
  - Distant Tumor Progression includes new or progression of pre-existing tumors outside of the lung using abdomen and pelvis CT, brain MRI, and extremity CT or MRI.
- Record any applicable AEs or SAEs:
  - Record any AEs or SAEs that may have occurred within 30 days of an ablation or re-ablation procedure.
  - Record only device- or procedure-related AEs or any SAEs that may have occurred after 30 days of an ablation or re-ablation procedure.

7.5 Visit 5 – 6-month Follow-up

Visit 5 occurs 6 months (± 1 month) after the ablation procedure. The subject will visit the study site for the following assessments:

- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic

steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Complete two validated quality of life questionnaires: EORTC QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.
- Obtain PFTs, which include 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).
- Complete chest CT, abdomen and pelvis CT, brain MRI (if site SOC), and extremity CT or MRI (if site SOC) to determine Tumor Progression. Contrast-enhanced images are preferred but not required. If a site takes a PET scan per SOC, the other images should also be taken, per protocol:
  - Local Tumor Progression (LTP), defined as recurrence of the originally ablated tumor(s) within or abutting the ablation zone using Chest CT and the 30-day post-ablation imaging as the baseline.
  - Regional Tumor Progression includes new or progression of pre-existing tumors that were not previously ablated within either lung using chest CT.
  - Distant Tumor Progression includes new or progression of pre-existing tumors outside of the lung using abdomen and pelvis CT, brain MRI, and extremity CT or MRI.
- Record any applicable AEs or SAEs:
  - Record any AEs or SAEs that may have occurred within 30 days of an ablation or re-ablation procedure.
  - Record only device- or procedure-related AEs or any SAEs that may have occurred after 30 days of an ablation or re-ablation procedure.

7.6 Visit 6 – 12-month Follow-up

Visit 6 occurs 12 months (± 1 month) after the first ablation procedure. The subject will visit the study site for the following assessments:

- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Complete two validated quality of life questionnaires: EORTC QLQ-C30 and the lung-specific QLQ-LC13. These questionnaires should be administered in person, during the study visit. However, they may be administered over the phone, when needed.
- Collect key vitals: blood pressure, heart rate, and pulse oximetry.
- Evaluate ECOG performance status.

- Obtain PFTs, which include 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).
- Complete chest CT, abdomen and pelvis CT, brain MRI (if site SOC), and extremity CT or MRI (if site SOC) to determine Tumor Progression. Contrast-enhanced images are preferred but not required. If a site takes a PET scan per SOC, the other images should also be taken, per protocol:
  - Local Tumor Progression (LTP), defined as recurrence of the originally ablated tumor(s) within or abutting the ablation zone using Chest CT and the 30-day post-ablation imaging as the baseline.
  - Regional Tumor Progression includes new or progression of pre-existing tumors that were not previously ablated within either lung using chest CT.
  - Distant Tumor Progression includes new or progression of pre-existing tumors outside of the lung using abdomen and pelvis CT, brain MRI, and extremity CT or MRI.
- Record any applicable AEs or SAEs:
  - Record any AEs or SAEs that may have occurred within 30 days of an ablation or re-ablation procedure.
  - Record only device- or procedure-related AEs or any SAEs that may have occurred after 30 days of an ablation or re-ablation procedure.

7.7 Unscheduled Visits

The following data will be collected during each unscheduled visit:

- Reason for the unscheduled visit.
- Document any changes or updates to the subject's relevant concomitant medications (blood thinning/anticoagulants, antiplatelets, opioids, systemic chemotherapy, systemic steroids, immunotherapies, anti-inflammatories, NSAIDs, antibiotics, and medications used to treat adverse events)
- Document any changes or updates to the subject's concomitant procedures.
- Record any applicable AEs or SAEs:
  - Record any AEs or SAEs that may have occurred within 30 days of an ablation or re-ablation procedure.
  - Record only device- or procedure-related AEs or any SAEs that may have occurred after 30 days of an ablation or re-ablation procedure.

8.0 DATA MANAGEMENT AND INTEGRITY

8.1 Data Completion and Record Keeping

Source Documents

Source documents are documents on which information regarding subjects is first recorded, including printed, optical, or electronic documents. Investigator subject files or hospital records generally are the basis of source document information. This includes, but is not limited to, the following: original subject files; hospital/clinic records; original recordings/tracing; digital images from automated instruments (e.g., cameras); radiographs; device accountability records; photographic negatives; and, records kept at the investigation site, at the laboratories, and at other departments involved in the clinical investigation. Assessments made by the central review committee that are directly entered into the CRFs may also be considered as source documents.

Other source data comes from NeuWave Medical's Call Home Database. The NEUWAVE FLEX Ablation System has a functionality that electronically collects procedure data and information during the ablation procedure and is transmitted by the NEUWAVE Ablation System to NeuWave Medical, Inc., after the conclusion of each ablation procedure; this information is collectively called the "Call Home Database." The procedure data include, but are not limited to, the following: date and time of procedure, anatomical location of ablations, number of ablation cycles and power used for each ablation, number of probe placement attempts per ablation, type of probes used, and type of anesthesia. Some of these relevant ablation procedure details will be provided to the site via a report generated from Call Home Database called a Call Home Report. The study site will review the report for accuracy and enter the procedure details into the study's clinical database. Reports generated from the Call Home Database must be retained by the Investigator as part of the subject's permanent medical record. The report should be retained for review and source data verification by the monitor. If a site is unable to receive the report generated from the Call Home Database, the relevant ablation procedure details should be manually recorded in the source documents from what is displayed on the NeuWave System monitor screen.

All applicable scans (i.e., cone beam CT scans (taken during the ablation procedure), all conventional CT scans (taken during the post-ablation follow-up visits), and applicable PET scans should be de-identified and uploaded to the study imaging database in DICOM (digital imaging and communications in medicine) format, if possible. The imaging database will be controlled and maintained by the same vendor that organized and contracted the Central Review Committee, [redacted] The Sponsor will have "read-only" access to the imaging database during the study. Separate instructions for the site to de-identify and upload all applicable scans will be provided in a separate document.

Also, only for those subjects who specifically consent, some ablation procedures may be filmed for training and educational purposes.

Source documents must be retained by the Investigator as part of the subject's permanent medical record. The information in the source documents is used to complete the eCRFs. All

information captured on the eCRFs should be completely and accurately supported in source documentation. Any additional information relevant to the study should be included in the source documents. Particularly, any deviations from the protocol or procedures should be recorded in the source documents. The Investigator will retain originals of all source documents, subject consent forms, and study data.

Electronic Data Capture

An EDC system will be used by site personnel to transfer data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application [redacted]. This system was designed and is developed and maintained by [redacted] in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The EDC system will be used to facilitate the collection of all data at the site. Designated site personnel will be responsible for entering subject data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function. An EDC digital User Manual will be available under the help menu within the [redacted] website to assist in the collection and entry of source data into the electronic casebook.

A 24/7/365 Help Desk Support line [redacted] staffed by the outsourced vendor will also be available to respond to site and monitor questions.

Data Collection

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each subject. The subject's unique study ID number will be visible on each eCRF. At no time should the subject's name appear on the eCRFs.

All data should be recorded accurately and completely. The Investigator is responsible for reviewing and approving each completed eCRF. The Investigator will document assurance of overall review and approval by electronically signing each subject's electronic casebook.

Data Correction

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by Sponsor reviewers. The change, the person making the change, and the time the change was made to the eCRFs will be automatically captured in the audit trail [redacted].

Data Privacy

The collection, use, and disclosure of all personal data, including subject health and medical information, are to be maintained in compliance with applicable personal data protection and security laws and regulations that govern protected health information and the informed consent given by each subject. When collecting and processing such personal data,

appropriate measures are to be taken to maintain the confidentiality of subject health and medical information and to prevent access by unauthorized persons.

None of the data collected and transmitted by Call Home Database is attributable to an identifiable subject.

Record Retention, Inspection, and Custody

The Investigator must maintain all documentation related to the study until notified by the Sponsor. The Investigator will allow representatives of the Sponsor, the FDA, or other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Study reports will not identify subjects by name. These reports may be submitted to the FDA and/or regulatory authorities.

If custody of the clinical study records is transferred, notice of such a transfer should be given to the Sponsor no later than 10 working days after the transfer occurs.

8.2 Medical Dictionary Coding

Medical dictionary coding of medical history and verbatim AEs captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug dictionaries will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

8.3 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during monitoring visits (onsite or offsite); any discrepancies will be resolved with the Investigator or designees, as appropriate.

8.3.1 Investigator Training

Prior to screening subjects for this study, the PI, sub-Investigators, study coordinators, and other designated staff (as applicable) will be provided information on study execution, data collection, and procedures specific to this clinical protocol. All training, and retraining, if necessary, will be documented accordingly and filed.

8.3.2 Monitoring

This study will be monitored by the Sponsor to ensure the following:

- The rights and well-being of the subjects are protected.
- The reported data is accurate, complete, and verifiable from source documents where utilized.
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local/regional regulatory

requirements.

The extent and nature of monitoring will be predetermined and agreed to by the Sponsor and investigators. Monitors will comply with established written standard operating procedures as well as procedures specified by the Sponsor for monitoring this study as characterized in the Monitoring Plan.

9.0 DEVIATIONS FROM THE PROTOCOL

A protocol deviation is any noncompliance with the registry protocol, Good Clinical Practice, or protocol-specific requirements. A deviation (any activity conducted outside the parameters established by the protocol) can be identified from a number of sources. Potential sources include but are not limited to: a member of the Investigator's staff, a Sponsor representative during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. Regardless of the source, it is crucial to document the deviation in the protocol deviation eCRF. The Investigator will report protocol deviations to the IRB/EC as required by the IRB/EC procedures.

Any deviation from the protocol or procedures should be recorded in the source documents. Assessments or visits that are not completed because they are not SOC at a site should not be considered protocol deviations if the protocol specifies that the assessment or visit is only to be collected if SOC.

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate. All deviations to the protocol requirements should be documented in the source as well as the protocol deviation eCRF.

10.0 STATISTICAL METHODOLOGY

10.1 Statistical and Analytical Plans

The Sponsor Data Management and Biostatistics groups will be responsible for the analysis of data from this protocol. A comprehensive and detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock to supplement the statistical design and analysis described in this section.

Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, median, minimum, and maximum.

10.2 Study Design

This is a prospective, multicenter, single-arm study.

10.3 Ablation Assignment

This is a single-arm study where all enrolled subjects will receive the same ablation procedure: transbronchial microwave ablation using the NEUWAVE FLEX MC Microwave Ablation System and Accessories for oligometastatic tumors (≤ 2cm) in the lung. There will be no blinding or randomization.

10.4 Interval Windows

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

10.5 Primary Endpoints and Associated Hypotheses

The following hypotheses will be evaluated in this study:

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

$$H_1: p > 0.80$$

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.

10.6 Levels of Significance

A one-sided significance level of 0.025 will be used to test the hypotheses above. No other formal hypothesis tests are planned for this study and estimation for all other endpoints will be performed using two-sided 95% confidence intervals.

10.7 Analysis Sets

The primary analysis of safety and effectiveness endpoints will be performed on the Full Analysis Set, defined as all subjects who are enrolled in the study and receive ablation. A Per Protocol analysis set will be defined as all subjects who have undergone the ablation procedure

and have no major protocol deviations. Effectiveness analyses will be repeated for the Per Protocol Set.

10.8 Sample Size Justification

[redacted]

10.9 Analyses to be Conducted

Analyses described below will be performed on all enrolled and ablated subjects.

Disposition of Study Subjects

Subject disposition will be summarized using counts and percentages. The number and percentage of subjects completed and discontinued along with the specific reasons for discontinuation will be tabulated by ablation group and in total.

Demographic and Baseline Characteristics

Summary statistics will be provided for subject demographics and pre-operative ablation characteristics.

Primary and Secondary Endpoint Analyses

The number and percentage of tumors achieving Technique Efficacy will be summarized and a 95% confidence interval will be estimated. Hypothesis testing for the primary endpoint will be performed using the methodology described in the previous section. The number and percentage of tumors achieving Technical Success will also be summarized, and a 95% confidence interval will be estimated. Local Tumor Progression will be summarized in a similar manner. Only target lesions will be included in the primary endpoint analysis for Technique Efficacy and primary summaries of Technical Success and local Tumor Progression. Data collected on non-target tumors for these endpoints will be summarized separately and not included as part of the primary analysis. The analysis of target tumors for these three endpoints will also include a subject level summary that will be secondary or supportive to the tumor level analysis.

Summary statistics will be provided for other secondary endpoints, as appropriate, for continuous or categorical variables. Local Tumor Progression Free Survival, Progression Free Survival, and Overall Survival will be estimated using the Kaplan-Meier method and confidence intervals will be provided.

[redacted]

The number and percentage of subjects experiencing perioperative AEs (time of consent through 30 days of any ablation procedure), device- and procedure-related AEs (30 days post any ablation procedure through the end of the study or early discontinuation) and all SAEs (time of consent through the end of the study or early discontinuation) 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 $\geq$ 2)
2. Hemorrhage, bleeding requiring medical intervention (CTCAE grade $\geq$ 2)
3. Chest wall pain
4. Pleural effusion or empyema (overall and requiring chest tube drainage)
5. Pneumonia
6. Pulmonary abscess
7. Other lower-tract respiratory infection

8. Bronchopleural fistula.

The Numeric Pain Rating Scale scores will be summarized with methodology consistent to the recommendations of the specific survey. Additional endpoints will be summarized with descriptive statistics.

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.

Complete details for all planned analyses will be included in the study SAP, which will be finalized prior to database lock.

Analysis of Safety

The analysis of safety is summarized above under Primary and Secondary Endpoint Analyses.

Handling of Dropouts or Missing Data

The primary endpoint analysis of Technique Efficacy at Visit 3 (30 days post-ablation) will be performed on observed data only. It is anticipated that dropout before the 30-day visit will be unlikely. However, several sensitivity analyses will be performed for the primary endpoint to assess the robustness of the conclusion based on observed data. This will include a worst-case assumption where all subjects not completing Visit 3 will be assumed to have not achieved Technique Efficacy. A tipping point analysis and multiple imputation will also be considered as alternatives to handling missing data. Time-to-event analyses will use standard censoring assumptions for the handling of subjects who do not complete follow-up visits. Complete details on sensitivity analyses for the primary and secondary endpoints will be provided in the SAP.

Analysis of Subgroups

At a minimum, subgroup analyses are planned to be performed by original histology and tumor size. Additional subgroups may be identified pending the distribution of baseline demographic or clinical characteristics. All subgroup analyses will be descriptive in nature and summary statistics will be provided for procedure-related parameters and time-to-event endpoints and adverse events.

11.0 RISKS AND BENEFITS OF THE STUDY

This study may or may not provide any benefits to the subject. However, the data collected throughout the study may help to assess the effectiveness and safety of a new ablation technique: robotic-assisted transbronchial microwave ablation of oligometastatic tumors in the lung.

Procedural Risks

The procedural risks associated with the FLEX MC transbronchial ablation procedure are expected to be similar to those associated with diagnostic bronchoscopy as well as those associated with thermal ablation, which in extremely rare instances could lead to death. The Sponsor plans on mitigating these risks during the clinical study by careful patient selection, implementing intraprocedural stopping rules, and the establishment of an independent DSMB to monitor the study.

Most commonly known risks for diagnostic bronchoscopy and thermal ablation procedures in the lung are summarized below by expected frequency: extremely rare (< 0.01%), rare (0.01% - 0.1%), uncommon (0.1% - 1%), common (1% - 10%), and very common (> 10%):

Known Risks for: Diagnostic Bronchoscopy	**Known Risks for: TransbronchialThermal Ablation Procedures in the Lung**
RARE: • Cardiovascular events UNCOMMON: • Breathing difficulty • Vocal cord spasm • Vomiting • Dizziness • Bronchial spasm (muscle contraction of the airway) • Hypoxemia (shortness of breath due to low levels of oxygen in the blood) COMMON: • Pneumothorax (when air leaks into the space between the lungs and the chest wall) • Hemorrhage (bleeding requiring medical intervention)	RARE: • Bronchopleural fistula (abnormal passageway that develops between the large airways in the lungs and the space that lines the lungs) UNCOMMON: • Air/Gas embolism (blockage or obstruction of a blood vessel) • Infection COMMON: • Pneumothorax (when air leaks into the space between the lungs and the chest wall) • Hemorrhage (bleeding requiring medical intervention) • Pleural effusion (buildup of fluid in tissues lining the lungs and the chest requiring tube drainage) • Pneumonia VERY COMMON

	• Pain • Post-ablation syndrome

Anesthesia Risks

Subjects will be put under general anesthesia for the study procedure. Common risks of anesthesia include nausea, vomiting, dizziness, drowsiness, and shivering. These are typically mild, short-lived symptoms that are easily managed. In rare instances, liver toxicity and cardiovascular events may occur.

Intubation Risks

There are some risks related to the intubation procedure as well as passing the bronchoscope into the airway. These rare risks include intubation-related airway injury, injury to teeth or dental work, bleeding, lung injury, and aspiration.

Radiation Risks

The required CT (computerized tomography) images will expose subjects to radiation. The total radiation exposure for each subject will be dependent on the number of CTs per subject and the type of CTs, as well as many other factors, such as the manufacturer of the scanning equipment. Conventional CT has an average radiation range 1mSv to 10mSv, while the average radiation range for cone beam CT is 1mSv to 5mSv. Recent pilot studies of bronchoscopic microwave ablation have reported a mean radiation dose of 27.8 mSv.[22] This is comparable to dose exposure seen in other common image guided procedures, such as percutaneous coronary intervention (15 mSv), atrial fibrillation ablation (17 mSv), and transcatheter aortic valve implantation (37 mSv).[29] The total radiation exposure to the subject during the ablation procedure will be captured.

Device Risks

The device risks associated with the FLEX MC procedure includes those of a diagnostic bronchoscopy as well as those associated with thermal ablation. These primarily include pneumothorax, unintended thermal damage, embolism, excessive bleeding, premature end of procedure, and in rare instances could lead to death. These risks have been identified and mitigated through the risk management tools compliant with ISO 14971 during the development of the MONARCH and the FLEX Systems. A summary of the more common device risks and design mitigations are listed below.

Device Risk	Design Mitigation(s)
Pneumothorax	MONARCH platform incorporates pre-procedure planning, facilitates multiple imaging modalities during navigation and direct visualization via camera in the MONARCH bronchoscope. The NEUWAVE FLEX probe tip is highly visible under imaging to allow proximity to the pleura to be assessed throughout the procedure.
Unintended thermal damage due to ablation zone shape	NEUWAVE FLEX System includes a Time-Power onscreen ex-vivo ablation zone reference for the user. NEUWAVE FLEX System uses CO_2 gas to cool the FLEX probe while continuously monitoring temperature at three locations on the probe.

Unintended thermal damage due to probe placement	MONARCH platform incorporates pre-procedure planning, multiple imaging modalities during navigation and direct visualization via camera in the MONARCH bronchoscope. The NEUWAVE FLEX probe is highly visible under imaging to allow probe location to be assessed throughout the procedure.
Embolism due to CO_2 cooling gas leak	NEUWAVE FLEX Probe is designed and tested to safely contain high pressure CO_2 gas in a sealed system. In addition, the user is required to perform a functional probe test that includes a CO_2 leak check. The system will not allow energy delivery if a leak is detected.
Excessive bleeding due to organ laceration	MONARCH facilitates multiple imaging modalities during navigation and includes direct visualization via camera in the MONARCH bronchoscope. NEUWAVE FLEX Probe tips are coated with non-stick material designed to reduce insertion/removal force and help prevent ablated tissue adhesion to the probe tip.

Benefits

In patients with a controlled primary malignancy who develop oligometastatic disease in the lung for which their treatment team believes local tumor control is necessary, FLEX MC provides a treatment option via complete tumor ablation. This option may minimize some of the risks associated with other options to achieve local control including surgery, SBRT, or percutaneous approaches. In addition, FLEX MC may offer patients less of a decrement in health-related quality of life as compared to other currently available therapies. The risks of FLEX MC are those associated with known risks of bronchoscopy and thermal ablation, which are well established procedures. With the existing robust risk mitigations in place (described above), the Sponsor's assessment is that the risks are adequately analyzed, evaluated, controlled, verified for effectiveness, and the benefits outweigh the risks in this patient population.

12.0 ASSESSMENT OF SAFETY

Subjects will be evaluated for AEs and SAEs from the time of consent based on the following descriptions:

- Perioperative AEs will be captured 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.
- AEs that are deemed related to the study device or procedure will be captured 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.

Investigators should remind study subjects to notify and/or see them or their study team first, when possible, if they experience any adverse events versus seeking treatment elsewhere.

Ongoing Review

The Sponsor will also review complications periodically, as per the study's Safety Management Plan.

12.1 Adverse Events

Adverse Event (AE)

For this study, an adverse event is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in a subject whether or not related to the study device or procedure.

Expected Morbidity/Anticipated Adverse Events

An expected morbidity/procedural complication is defined as an AE that is known to be common or usual in nature, severity, or incidence during ablation of the lung.

Serious Adverse Event (SAE)

It is the Investigator's responsibility to determine the "seriousness" of an AE using the protocol defined terms below. An SAE is an AE that results in one or more of the following for this study:

- Death;
- Serious deterioration in the health of the subject that resulted in any of the following:
    - Life threatening illness or injury;
    - Permanent impairment of a body structure or a body function;
    - Hospitalization or prolongation of patient hospitalization;
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
    - Chronic disease.

- Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect.

Notes:

1. Progression of the disease under study should not be reported as an SAE.
2. "Death" should not be reported as an AE. The cause of death should be reported as an AE. The only exception is "Sudden Death" when the cause is unknown.
3. Planned hospitalization for a pre-existing condition should not be considered an SAE.
4. A procedure required by the protocol should not be considered an SAE, unless the subject experiences a serious deterioration in health or hospitalization is prolonged.

The Sponsor will review all applicably reported AEs and SAEs according to the current Safety Monitoring Plan.

Unanticipated Adverse Device Event (UADE)

Any SAE caused by, or associated with, the device, if that event was not previously identified in nature, severity, or degree of incidence in the protocol or Investigator Brochure, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

Investigators are required to submit a report of a UADE to the Sponsor and the reviewing IRB as soon as possible, but no later than **72 hours** after the investigator first becomes aware of the event.

Sponsors must immediately conduct an evaluation of a UADE and report the results of the evaluation to FDA, all reviewing IRBs/ECs, and participating investigators within **10 working days** after the Sponsor first receives notice of the event.

SEVERITY OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the severity of an AE. AE severity in this study will be determined using the current version of the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE uses Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guidelines, provided below. Please note that a change in severity, or grade, may constitute a new reportable AE.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g., bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- Grade 4: Life-threatening consequences; urgent intervention indicated; and
- Grade 5: Death related to AE.

Note: A semi-colon indicates "or" within the description of the grade.

RELATIONSHIP OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the relationship between all AEs and SAEs and the study procedure and device. The following guidelines should be used in determining the relationship of an AE to a device, study procedure, or other causality:

Not Related	Relationship to the device or procedure can be excluded when: • The event has no temporal relationship with the use of the device or the procedures related to the device; • The event does not follow a known response pattern to the device or procedure (if the response pattern is previously known) and is biologically implausible; • The discontinuation of the device application or the reduction of the level activation/exposure (when clinically feasible) and reintroduction of its use (or increase of the level of activation/exposure), does not impact the event; • The event involves a body-site or an organ that cannot be affected by the device or procedure; • The event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); and • The event does not depend on a false result given by the device used for diagnosis, when applicable. Note: To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.
Possible*	The relationship with the use of the device or procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/condition and/or an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable*	The relationship with the use of the device or procedure seems relevant and/or the event cannot reasonably be explained by another cause.
Causal Relationship*	The event is associated with the device or with procedure beyond reasonable doubt when:

	• The event is a known side effect of the product category the device belongs to or of similar device and procedures;
	• The event has a temporal relationship with the device uses/application or procedures;
	• The event involves a body-site or organ that:
	  ▪ The device or procedures are applied to; or
	  ▪ The device or procedures have an effect on.
	• The event follows a known response pattern to the device (if the response pattern is previously known);
	• The discontinuation of the device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
	• Other possible causes (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment) have been adequately ruled out;
	• Harm to the subject is due to error in use; and
	• The event depends on a false result given by the device used for diagnosis, when applicable.
	To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.

*Indicates definitions of relationship that qualify to be recorded as part of the study for AEs only that occur more than 30-days any ablation procedure. All SAEs, regardless of relationship, will be collected.

12.2 Reporting Adverse Events

The Investigator is required to report all applicable non-serious AEs to the Sponsor within **14 days** of becoming aware of the event.

All SAEs and UADEs, regardless of relationship to the study device or procedure, are to be reported as soon as possible, but no later than **72 hours** after becoming aware of the event.

The study site will report applicable AEs and all SAEs to the Sponsor by entering the event into the EDC system via the AE eCRF, which will trigger an automated email to the Sponsor. Additional information, including the Investigator's assessment, may be added to the eCRF later. Any necessary medical management of the event will be recorded in the subject's medical record/source document. If the Sponsor requires supporting documentation or other information, the Sponsor will contact the study site.

Data related to AEs and SAEs will be collected until event resolution, until the event is considered stable, or until all attempts to determine the resolution of the event are exhausted.

All AEs and SAEs that are unresolved at study completion (or early termination) will be recorded as ongoing at study end.

The report of an AE or SAE by a site does not constitute an admission that study personnel or the user facility (hospital/clinic) caused or contributed to the event. The study site is responsible for submitting AEs/SAE to the reviewing IRB/EC, per their IRB/EC procedures.

In addition, the following information should be recorded:

- Onset date.
- Resolution date or date of death.
- Severity of the event.
- Action taken.
- Event status (ongoing at study end or resolved).
- Relationship of AE to the study devices.
- Relationship of AE to the study procedures.
- Indication of seriousness.
- Was AE anticipated.
- Time of AE (navigation, pre-ablation probe placement, ablation, post-ablation).

A report of a subject death or severe hemorrhage requiring intervention beyond local therapy (i.e., Nashville $\geq$ grade 2 or CTCAE $\geq$ grade 2) within 30 days of tumor ablation procedure will put enrollment on hold and require an investigation to determine if the death or hemorrhage was related to the ablation procedure. The investigation will be led by the independent Data Safety Monitoring Board, DSMB, described in Section 12.3.

Based on ongoing reviews of the data, additional stopping rules may be introduced as deemed appropriate.

12.3 Data Safety Monitoring Board

An independent 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 $\geq$ grade 2 or CTCAE $\geq$ 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.

A document outlining membership and responsibilities will be described in detail in a separate charter, which will be finalized prior to the first subject being ablated.

13.0 PRODUCT COMPLAINT DEFINITION

A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, labeling, quality, durability, reliability, safety, effectiveness, or performance of a device (21CFR 820.3 (b)). A product complaint may or may not be associated with an AE/SAE.

Product complaints may include, but are not limited to:

1. Product contamination;
2. Defective components;
3. Poor packaging or product mix-up;
4. Device malfunction (the failure of a device to perform as intended for this study);
5. Labeling concerns; and
6. User errors.

Reporting Product Complaints

All product complaints, malfunctions, or failures related to devices in the procedure (including both NeuWave and Auris devices) shall be documented in the Product Complaints eCRF in a timely manner after becoming aware of the event. The eCRF completion will trigger an automated notification email to the Sponsor.

The device involved in the complaint should be retained on site. A Sponsor representative will organize collection of the device for evaluation, as needed.

14.0 TRAINING

All investigators (PIs or Sub-Investigators) who will be performing the FLEX MC ablation procedure are required to undergo FLEX MC Training. The training will include lectures on microwave ablation of the lung, probe placement, margin planning and assessment, and review of cases from the previous Sponsor study on transbronchial microwave ablation using the FLEX System.[23] The training will also involve a human, simulated, or synthetic tissue lab to demonstrate the FLEX MC workflow, probe placement using augmented fluoroscopy and CBCT confirmation, scope and probe retraction workflow, and reading post-ablation CBCT images. A FLEX MC Training Completion Form will be signed upon completion of the training course and filed in the Investigator Site File.

In addition to the training, per the Investigator Selection Criteria, all investigators who will be performing the FLEX MC ablation procedure are also required to complete a minimum of 20 MONARCH diagnostic bronchoscopy procedures, with at least five of those cases using CBCT, and demonstrate proficiency prior to enrolling subjects into the trial.

The Sponsor will provide access to a Product Development Specialist and/or a Medical Specialist experienced in this procedure for the treating physician during the case, as needed. This will be mandatory for the first case at each site and may be continued at the request of the site PIs for subsequent cases.

If MONARCH is not commercially available at a site to complete the required minimum 20 diagnostic bronchoscopy procedures (with at least five of those cases using CBCT), the investigator may complete these required lead-in cases, under this protocol per the MONARCH IFU/User Manual. Subjects will consent for their diagnostic bronchoscopy as a lead-in case for this study. Lead-in cases are not treated (ablated) with the FLEX MC device at the time of the diagnostic procedure. Should the patient later qualify for the FLEX MC study, the patient will then be consented for FLEX MC study participation.

After the diagnostic bronchoscopy with MONARCH, the investigator will follow these subjects to the first follow up time point per the site's SOC (either telephone call or clinical visit), or within 7 days, to note any potential adverse events related to the diagnostic procedure, which will be reported the same way as the FLEX MC adverse events. Any data collected from these lead-in cases will be in support of appropriate event reporting.

The investigator may also perform additional "lead-in" diagnostic cases during the course of the study enrollment, if deemed warranted by the investigator to maintain proficiency with the MONARCH and/or CBCT workflow.

15.0 DATA AND PUBLICATION POLICIES

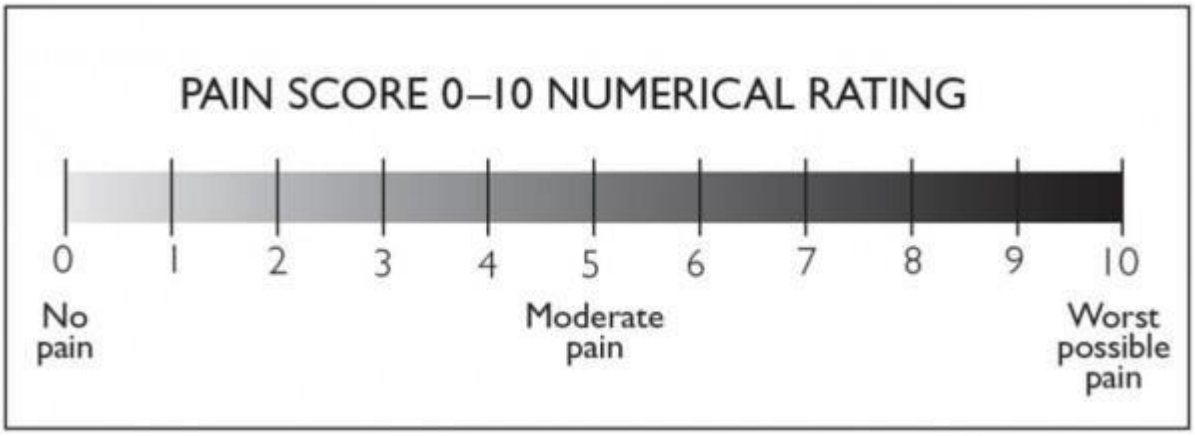
Publication and authorship policies should be determined and aligned with the clinical study agreement executed between the operating company and the clinical site. Publication of the results of this study will be governed by Johnson & Johnson publication policies, including current and applicable Medical Device Publication Policy. Any presentation, abstract, or manuscript will be made available for review by the Sponsor prior to submission. Licensing agreements or copyrights applying to tools, work products or intellectual property used during the study should be observed and clearly displayed on study documentation and publications, wherever appropriate.

All manuscripts of data obtained from this clinical study will be reviewed and approved by the Sponsor, and each author, prior to any submission. Current and applicable Medical Device Publication Policy will be followed. The Sponsor will require a written agreement for any external author(s) prior to initiating any publication. All authors must disclose financial or personal affiliations that could be considered a conflict of interest.

16.0 SUPPLEMENTS

16.1 Appendix 1: Numeric Pain Rating Scale

The Numeric Pain Rating Scale can be administered verbally (therefore also by telephone) or graphically for self-completion. Administers will ask respondents to “indicate the numeric value on the segmented scale that best describes their pain intensity right now with 0 being NO PAIN, 5 being MODERATE PAIN, and 10 being WORST POSSIBLE PAIN”.



16.2 Appendix 2: Nashville Scale for Bleeding

Grade	Findings at Bronchoscopy	Rationale
1	Suctioning of blood required for less than 1 minute	Minimal bleeding of no clinical consequence to the patient or the provider.
2	Suctioning more than 1 minute required or repeat wedging of the bronchoscope for persistent bleeding or instillation of cold saline, diluted vasoactive substances or thrombin	Requirement of one or more tools to control or prevent further bleeding.
3	Selective intubation with ETT or balloon/bronchial blocker for less than 20 minutes. Or premature interruption of the procedure.	Meaningful but short-term change in the clinical status of the patient involving more invasive procedures and causing interruption of the planned procedure.
4	Persistent selective intubation > 20 minutes or new admission to the ICU or PRBC transfusion or need for bronchial artery embolization or resuscitation.	Change in level of care and requiring advanced ventilatory support and/or transfusion of PRBC.

16.3 Glossary

Acronyms/ Abbreviations	Terms
ADL	Activities of Daily Living
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
BMI	Body Mass Index
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CO2	Carbon Dioxide
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DICOM	Digital Imaging and Communications in Medicine
DLCO	Diffusing [capacity of the] Lung [for] Carbon Monoxide
DSMB	Data Safety Monitoring Board
EBRT	External Beam Radiation Therapy
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EKG	Electrocardiogram
ENB	Electromagnetic Navigation Bronchoscopy
EORTC	European Organization for the Research and Treatment of Cancer
EWC	Extended Working Channel
FDA	Food and Drug Administration
FEF	Forced Expiratory Flow
FEV1	Forced Expiratory Volume
FRC	Functional Residual Capacity

Acronyms/ Abbreviations	Terms
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HRQOL	Health-Related Quality of Life
IB	Investigator Brochure
ICF	Informed Consent Form
ID	Identification
IDE	Investigational Device Exemption
IFU	Instructions for Use
IGTA	Image-Guided Thermal Ablation
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LOS	Length of Hospital Stay
LTP	Local Tumor Progression
LTPFS	Local Tumor Progression Free Survival
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PAP	Positive Airway Pressure
PDM	Power Distribution Module
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PI	Principal Investigator
PT	Prothrombin Time

Acronyms/ Abbreviations	Terms
RAB	Robotic-Assisted Bronchoscopy
RFA	Radiofrequency Ablation
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBRT	Stereotactic Body Radiation Therapy
SOC	Standard of Care
SPO2	Oxygen Saturation
TLC	Total Leukocyte Count
UADE	Unanticipated Adverse Device Event
US	United States

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