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A Multicenter Study of the NEUWAVE Flex Microwave Ablation System in the Ablation of Medically Inoperable Primary Soft Tissue Lesions of the Lung: An Initial Experience

Sponsor Protocol Number: NEU_2017_06

Document	Effective Date
Original (version 1.0)	25 Jan 2018
Amendment 1 (version 2.0)	08 Jun 2018
Amendment 2 (version 3.0)	25 Jul 2018

Sponsor: NeuWave Medical, Inc.
3529 Anderson Street Madison WI 53704

Sponsor's Medical Directors: [redacted]

Name of Finished Product: NEUWAVE Flex Microwave Ablation System and Accessories

CONFIDENTIALITY STATEMENT

Johnson & Johnson MEDICAL DEVICES

Sponsor Signature

Protocol Number:	NEU_2017_06
Protocol Title:	A Multicenter Study of the NEUWAVE Flex Microwave Ablation System in the Ablation of Medically Inoperable Primary Soft Tissue Lesions of the Lung: An Initial Experience
Protocol Amendment 2 Date:	25 Jul 2018

Signature:

[redacted] Date

This study will be performed in compliance with Good Clinical Practice (and in accordance with the Declaration of Helsinki), as well as all applicable local regulations.

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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 Practices (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 (where required).

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
Printed Name of Principal Investigator	

PLEASE RETAIN THE ORIGINAL SIGNED COPY FOR YOUR STUDY RECORDS

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1.0 SYNOPSIS

Full title & protocol number	A Multicenter Study of the NEUWAVE Flex Microwave Ablation System in the Ablation of Medically Inoperable Primary Soft Tissue Lesions of the Lung: An Initial Experience NEU_2017_06
Short title	NEUWAVE Flex Microwave Probe in Medically Inoperable Primary Soft Tissue Lesions of the Lung
IDE/IND number	N/A
Sponsor	NeuWave Medical, Inc.
Indication	Medically inoperable primary soft tissue lesions of the lung
Study article description	NEUWAVE Flex Microwave Ablation System and Accessories [redacted]
Regulatory classification	Registered devices used in the clinical trials: Class 2: NEUWAVE Flex Microwave Ablation System and Accessories [redacted]
Study devices and descriptions	NEUWAVE Flex Microwave Ablation System and Accessories (henceforth called NEUWAVE Flex Microwave Ablation System) are substantially equivalent to the marketed device, Certus 140 2.45 GHz Ablation System and Accessories. The device is designed for ablations of lesions in soft tissue in which the target tissue is accessed transbronchially. [redacted]

	[redacted]
Study design	Multicenter, single-arm
Sample size	No formal hypotheses are being tested in this study and hence a target sample size of 40 patients [redacted] is deemed adequate for a preliminary investigation of the feasibility of this procedure as well as for providing sufficient information for appropriately sizing a subsequent study.
Study population	Adult patients with a medically inoperable primary soft tissue lesion of the lung ≤ 2 cm located in the outer two-thirds and not closer than 1 cm to the pleura. Outer two-thirds of the lung is defined as peripheral beyond the segmental airway, past the segmental bronchi, such that proximal endobronchial soft tissue lesions are avoided; soft tissue lesions should not be contiguous with the pleura. This study may include patients with operable lesions, but who elect not to have surgery.
Geographic areas to be included	United States
Study duration	Enrollment: 1 year / Follow-up: 1 year
Procedure(s) description	[redacted]

	[redacted]
Primary objective	The primary objective of the study is to evaluate the NEUWAVE Flex Microwave Ablation System and Accessories in transbronchial ablation procedures for adult patients with a medically inoperable primary soft tissue lesion, based on the following assessments: 1. Device user experience survey 2. Technical success 3. Technique efficacy. Device user experience will be collected from the treating physician who will complete the User Experience Survey following each ablation procedure throughout the study, when applicable; the User Experience Survey is available as a separate document. The questionnaire includes, but is not limited to procedure workflow and the user's assessment on ease/difficulty of using the device. The User Experience Survey will augment the Product Development Specialist's understanding of the usability of the NEUWAVE Flex Microwave Ablation System and determine which enhancements, if any, are needed in the future. Technical success and technique efficacy will also be measured.
Secondary objectives	1. To evaluate safety through the monitoring of all device-related, procedure-related, and serious adverse events (SAEs) from start of ablation through

	1-year post-ablation. 2. To establish device and procedure effectiveness by following patients for 1-year post-ablation to ensure completeness and durability of treatment effect, based on standard endpoints in microwave ablation studies, as follows: a. Primary efficacy rate b. Secondary efficacy rate c. Target lesion recurrence 3. To calculate length of hospital stay (LOS), measured from post-ablation to discharge. 4. To calculate hospital readmission rate, defined as any readmission to the hospital within 30 days of the ablation procedure (Visit 2A).
Exploratory objectives	1. To assess the quality of life post microwave ablation of the lung throughout the 1 year ± 1 month follow-up period. 2. To assess the level of pain during the initial 30 days ± 7 days post-ablation.
Primary endpoints	• Device user experience: The data will come from the User Experience Survey, which will be completed by the treating physician following each ablation procedure. • Technical success, defined as: ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by cone beam CT imaging, immediately following the procedure. • Technique efficacy, defined as: ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed using CT imaging at Visit 3, which is 30 days ± 7 days after the first ablation procedure.

Secondary endpoints	The secondary endpoints, include the following: • Any complications attributable to the procedure, including all device-related, procedure-related, and SAEs, evaluated from the start of ablation through 30 days ± 7 days post-ablation and from the start of ablation through end of follow-up (1-year post-ablation) or early discontinuation. • Primary efficacy rate, defined as: the percentage of target soft tissue lesions successfully eradicated following the first ablation procedure, as assessed using CT imaging. • Secondary efficacy rate, defined as: the percentage of soft tissue lesions that have undergone successful repeat ablation following identification of local soft tissue lesion progression, as assessed using CT imaging. • Target lesion recurrence, defined as reappearance of the lesion at the treated site, as assessed using CT imaging. • LOS, measured from post-ablation to discharge. • Hospital readmission rate, defined as any readmission to the hospital within 30 days.
Exploratory endpoints	• Quality of life (QOL) questionnaires utilizing the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung-specific QLQ-LC13 to be completed at Screening (Visit 1), pre-ablation (Visit 2A), on Day 1 just prior to discharge (Visit 2B), and at all follow-up visits (Visit 3 through Visit 5). • Numeric Pain Rating Scale, to be completed at Screening (Visit 1), pre-ablation (Visit 2A), on Day 1 just prior to discharge (Visit 2B) and at 30 days ± 7 days post-ablation (Visit 3).
Inclusion criteria	1. Signed informed consent. 2. Patients ≥ 18 years old. 3. Performance status 0-2 (Eastern Cooperative Oncology Group classification [ECOG]). 4. Willing to fulfill all follow-up visit requirements. 5. Medically inoperable primary soft tissue lesion of the lung or patient election not to have surgery. (Medically inoperable is defined per the following indicators: post op predictive FEV1 < 40%; DLCO < 40%; hypoxemia or hypercapnia diabetes with end-organ damage; or severe cerebral, cardiovascular, peripheral vascular disease, or chronic heart disease).

	6. A soft tissue lesion ≤ 2 cm in the outer two-thirds of the lung and not closer than 1 cm to the pleura. Lesion size must be measured with at least 2-dimensional (2D) imaging. Only one lesion meeting the inclusion criteria may be treated during the day of ablation (Visit 2A). However, additional primary disease lesions may be present on the day of ablation. (Outer two-thirds of the lung is defined as peripheral beyond the segmental airway, past the segmental bronchi, such that proximal endobronchial soft tissue lesions are avoided; soft tissue lesions should not be contiguous with the pleura).
Exclusion criteria	1. Scheduled concurrent procedure for the target soft tissue lesion other than those that are lung related. 2. Pregnant or breastfeeding. 3. Physical or psychological condition that would impair study participation. 4. Patients with uncorrectable coagulopathy at time of screening. 5. Patient with implantable devices, including pacemakers or other electronic implants. 6. Prior pneumonectomy or bronchiectasis. 7. Severe neuromuscular disease. 8. Platelet count ≤ 50,000/mm^3. 9. ASA (American Society of Anesthesiologists) score of ≥ 4. 10. Inability to tolerate anesthesia. 11. Expected survival less than 6 months. 12. Clinically significant hypertension. 13. 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.) 14. Endobronchial soft tissue lesions proximal to the segmental airways. 15. CP-EBUS lymph node sampling that results in a positive diagnosis of malignancy. 16. Imaging findings of active pulmonary infection. 17. The patient was judged unsuitable for study participation by the Investigator for any other reason.

<table>
<tr><td>Test product</td><td>
<table>
<tr><th colspan="2">NEUWAVE Flex Microwave Ablation System</th></tr>
<tr><th>Product Code</th><th>Description</th></tr>
<tr><td>NWF1US1N</td><td>NEUWAVE Flex Microwave Ablation System, 120 Vac DR-000770</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
<tr><td>Safety assessments</td><td>Patients will be evaluated for AEs and SAEs at every study visit until the end-of-study, which is 1 year following the first ablation procedure.</td></tr>
<tr><td>Statistical analysis</td><td>Summary statistics will be provided for all endpoints collected. Analyses described below will be performed on the pooled set of 40 patients [redacted]

Responses to the User Experience Survey will be summarized with descriptive statistics appropriate for categorical or continuous variables.

The number and percentage of patients achieving technical success will be summarized and a 95% confidence interval will be estimated. Technique efficacy, as well as primary and secondary efficacy rates and hospital readmission rate, will be summarized in a similar manner. Local soft tissue lesion recurrence rates will be estimated using the Kaplan-Meier method and 95% confidence intervals will be provided.

The number and percentage of patients experiencing AEs from the start of ablation (Visit 2A) to Visit 3 (the first post-ablation visit) will be summarized by MedDRA preferred term and system organ class. A similar summary will also be provided for AEs that are device related and procedure related, and all SAEs. Ninety-five percent confidence intervals may be provided for pre-specified AEs of interest. These summaries will be repeated for the entire observation period (Visit 2A through study completion).

EORTC QOL questionnaires and Numeric Pain Rating Scale scores will be summarized with methodology consistent to the</td></tr>
</table>

	recommendations of the specific survey. Additional endpoints will be summarized with descriptive statistics.
Interim analysis	There are no plans for interim analyses, whose intent would be to stop the study early or to modify the study design. Two analysis timepoints are planned. The first analysis will occur after all patients [redacted] complete Visit 3 (30 days ± 7 days after the first ablation procedure). This analysis will provide a summary of the User Experience Survey, technical success, technique efficacy, and safety through Visit 3. When the second group completes this timepoint, results will be summarized for that group and subsequently in total. The second analysis timepoint will be at the completion of the study.
Ongoing review	The Sponsor will also review complications periodically, as per the Safety Management Plan. [redacted] A report of death will stop enrollment and require an investigation to determine if the death is related to the ablation procedure or device. If the death is deemed not related to the ablation procedure or device, the study may resume enrollment.
Data Safety Monitoring Board	A Data Safety Monitoring Board (DSMB) will be appointed by the Sponsor to review, on a regular basis, safety data from the study. The DSMB will advise the Sponsor regarding the continuing safety of patients and those yet to be recruited to the study. Based on accumulating 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 40 patients, 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.
Schedule of Assessments	See Table 1 on the next page.

Table 1: Schedule of Assessments

Visit No.	Visit 1:	Visit 2A	Visit 2B	Visit 3	Visit 4	Visit 5	Unscheduled Visit[23]
Visit	Screening	Ablation	Discharge[22]	Follow-up	Follow-up	Follow-up	
Interval Windows: Study Assessments	≤ 30 days preablation	Day 0 Ablation	Day 1	30 days (± 7 days)	6 months (±1 month)	12 months (±1 month)	
Study Assessments							
Informed consent[1]	X						
Demographics	X						
Medical/surgical history/ASA score[2]	X						
ECOG status and BMI[3]	X	X*	X	X	X	X	
Concomitant medications[4]	X	X	X	X	X	X	X
Serum pregnancy test	X						
Inclusion/exclusion criteria[5]	X	X*					
EORTC QOL[6]	X	X	X	X	X	X	
Numeric Pain Rating Scale	X	X*	X	X			
Administer antibiotics		X*					
Convex Probe (CP)-EBUS[7]		X					
Lesion details via CT	X[8]	X[9]		X[10]	X[10]	X[10]	
Pulmonary function tests (PFTs)[11]	X				X	X	
CBC with differentials	X			X	X	X	
Coagulation tests[12]	X			X	X	X	
Relevant genetic markers[13]	X						
Ablation procedure details[14]		X					
Device user experience[15]		X					
Technical success assessment[16]		X					
Technique efficacy assessment[17]				X			
Concomitant procedures (all)		X	X	X	X	X	X
AEs/SAEs[18]		X	X	X	X	X	X
Length of hospital stay[19]/ UB-04 data[20]			X				
Assess if hospital readmission [21]				X			

*** Indicates assessments should be done prior to the ablation procedure.**

[redacted]

[redacted]

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2.0 GLOSSARY

Table 2. Acronyms/ Abbreviations

Acronyms/ Abbreviations	Terms
AE	adverse event
ASA	American Society of Anesthesiologists
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CP-EBUS	convex probe endobronchial ultrasound
CT	computed tomography
CTC	Common Terminology Criteria
DICOM	digital imaging and communications in medicine
DLCO	diffusing [capacity of the] lung [for] carbon monoxide
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ENB	electromagnetic navigation bronchoscopy
EORTC	European Organization for Research and Treatment of Cancer
EWC	extended working channel
FeNO	fractional exhaled nitric oxide (test)
FEV1	forced vital capacity (FVC)
GCP	Good Clinical Practices
ICF	informed consent form
ICLS	Imaging Core Lab Services, LLC
ID	identification
IFU	instructions for use
INR	international normalized ratio

Acronyms/ Abbreviations	Terms
IRB	institutional review board
LOS	length of (hospital) stay
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	nonsteroidal anti-inflammatory drugs
PAP	positive airway pressure
PDM	power distribution module
PET	positron emission tomography
PFT	pulmonary function test
PI	principal investigator
PTA	plasma thromboplastin antecedent
PTT	partial prothrombin time
QOL	quality of life
SAE	serious adverse event
SOC	standard-of-care

3.0 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 that 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 in approximately 4 to 8 study sites in the United States under a single protocol approved by each participating site's IRB/EC prior to implementation. The principal investigator at each study site 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 (Medidata® Rave, 350 Hudson Street, 9th Floor, New York, New York, 10014). This system was designed and is developed and maintained by Medidata 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 IRB/EC as per their local requirements.

4.0 INTRODUCTION

There is clinical and economic demand for a minimally invasive treatment of pulmonary soft tissue lesions where tissue sparing is maximized, morbidity of the procedure is minimized, and the quality of care is most cost effective. Lung interventionalists desire a non-surgical approach that could allow both diagnosis and treatment in the shortest time frame possible while providing a proven durable effect. The flexible ablation platform provides a first-of-kind, minimally invasive, tissue-sparing bronchoscopic approach to lung tissue ablation.[1]

This study will establish the first experience with the use of the NEUWAVE Flex Microwave Ablation System in transbronchial ablation procedures. This study will also provide indications of the durability of ablation of soft tissue lesions with NEUWAVE Flex Microwave Ablation System.

In this protocol, the target tissue will be accessed using the flexible probe via an endobronchial approach.

In the device labeling, ex-vivo ablation size data is provided for lung, liver, and kidney tissue as a guide to users.

Although the ablation of lung lesions that are accessed transbronchially was anticipated and accounted for in the design and development of this device, the specific application of transbronchial ablation of lung lesions has not been reported to date in human subjects.

Per FDA Guidance: Use of Real World Evidence to Support Regulatory Decision Making for Medical Devices, this study is considered IDE Exempt because:

1. The device is being used in the normal course of medical practice under the authority of a healthcare provider.
2. The protocol does not dictate or influence treatment decisions.
3. The gathering of data per the protocol does not influence treatment decisions. All data gathered per this protocol are data that are normally collected and documented for ablation procedures.

For pulmonary soft tissue lesions, microwave ablation is believed to be a better treatment choice than radiofrequency (RF) ablation. Aerated lung is characterized by high impedance to electric current flow and poor heat transfer compared with most solid organs. The high impedance of normal lung tissue surrounding a soft tissue lesion can reduce power delivery, whereas poor thermal diffusion limits growth of the ablation zone.[2]

3

It should be noted that nearly all previous studies of microwave ablation passed the ablation probe into the lungs percutaneously, that is, through a needle puncture of the skin. In our proposed study, the microwave ablation probe is guided through the bronchial airway into the outer two-thirds of the lung.

A clinical study in humans found that the endobronchial approach limits complications. The rates of common complications were generally lower among those who had undergone endobronchial lung biopsy compared with those who had undergone percutaneous lung biopsy. The complications included pneumothorax, pleural effusion, hemoptysis, infection, pain, and bronchopleural fistula.[4] The endobronchial access, versus transthoracic penetration, of the probe is designed to minimize the risk of bronchopleural fistula. In addition, it is expected that ablations with the NEUWAVE Flex Microwave Ablation System will be a relatively quick procedure by overcoming perfusion and produce an effective volume to ablate the soft tissue lesions with a clinically beneficial margin.[5]

5.0 STUDY OBJECTIVE

5.1 Primary Objectives

The primary objective of the study is to evaluate the NEUWAVE Flex Microwave Ablation System in transbronchial ablation procedures for adult patients with a medically inoperable primary soft tissue lesion, based on the following assessments:

a. Device user experience survey
b. Technical success
c. Technique efficacy

Device user experience will be collected from the treating physician who will complete the User Experience Survey following each ablation procedure throughout the study, when applicable; the User Experience Survey is available as a separate document. The questionnaire will focus on procedure workflow and the user's assessment on ease/difficulty of using the device. The device user experience will augment the Product Development Specialist's understanding of the usability of the Flex system and determine which enhancements, if any, are needed.

5.2 Secondary Objectives

The secondary objectives are the following:

1. To evaluate safety through the monitoring of device-related and procedure-related advserse events (AEs) and all serious adverse events (SAEs), from start of ablation through 1-year post-ablation.
2. To establish device and procedure effectiveness by following patients for 1-year post-ablation to ensure completeness and durability of treatment effect, based on standard endpoints in microwave ablation, as follows:
   a. Primary efficacy rate
   b. Secondary efficacy rate
   c. Local soft lesion recurrence
   d. Length of hospital stay (LOS)
   e. Hospital readmission rate.
3. To calculate length of hospital stay (LOS), measured from post-ablation to discharge.
4. To calculate hospital readmission rate, defined as any readmission to the hospital within 30 days of the first ablation procedure (Visit 2A).

5.3 Exploratory Objectives

The exploratory objectives are the following:

1. To assess the quality of life post microwave ablation of the lung throughout the 1 year ± 1 month follow-up period.
2. To assess the level of pain during the initial 30 days ± 7 days post-ablation.

6.0 ENDPOINTS

6.1 Primary Endpoints

The primary endpoints include the following:

- Device user experience: The data will come from the User Experience Survey, which will be completed by the treating physician following each ablation procedure.
- Technical success, defined as: ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by cone beam CT imaging, immediately following the procedure.
- Technique efficacy, defined as ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus and ablative margin). Technique efficacy will be assessed using CT imaging at Visit 3, which is 30 days ± 7 days after the first ablation procedure.

6.2 Secondary Endpoints

The secondary endpoints include the following:

- Any complications attributable to the procedure, including all device-related, procedure-related, and serious adverse events (SAEs), evaluated from the start of ablation through 30 days ± 7 days post application of ablation and from the start of ablation through end of follow-up (1-year post-ablation) or early discontinuation.
- Primary efficacy rate, defined as the percentage of target soft tissue lesions successfully eradicated following the ablation procedure, as assessed using CT imaging.
- Secondary efficacy rate, defined as the percentage of soft tissue lesions that have undergone successful repeat ablation following identification of local soft tissue lesion progression, as assessed using CT imaging.
- Target lesion recurrence, defined as reappearance of the lesion at the treated site, as assessed using CT imaging.
- Length of stay, measured from after the ablation procedure until the patient is discharged home.
- Hospital readmission rate, defined as any readmission to the hospital within 30 days.

6.3 Additional Measurements / Data Collected

- Patient demographics and baseline characteristics.
- Quality of life (QOL) and pain.
- Relevant medical and surgical history.
- [redacted]Soft tissue lesion details (size, lesion type, location, shape). [redacted]

[redacted]

7.0 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan – Description

This is a multicenter, single-arm study for NEUWAVE Flex Microwave Ablation System in the ablation of soft tissue lesions of the lung for medically inoperable patients or those who elect not to have surgery. An experienced interventional pulmonologist or thoracic surgeon will determine whether a patient is "medically inoperable." Indicators defining medically inoperable are, as follows: post-op predictive FEV1 < 40%; DLCO < 40%; hypoxemia or hypercapnia diabetes with end-organ damage; or, severe cerebral, cardiovascular, peripheral vascular disease, or chronic heart disease.

Prospective patients will be informed about the nature of the research, given the ICF to read, and if the patient 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. Patients will be followed for approximately 1 year following the first ablation procedure for safety and efficacy outcomes.

[redacted] Only participants who withdraw or are terminated prior to the planned intrabronchial flexible probe ablation procedure will be replaced.

[redacted]

The study will end when all patients have completed the 12-month, post-ablation follow-up period or have withdrawn early.

7.2 Enrollment

A target total of approximately 40 patients, [redacted] will be enrolled across multiple study sites in the United States. A subject who signs the consent is considered screened and once treated they are considered enrolled into the study.

7.3 Inclusion Criteria

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

1. Signed informed consent.
2. Patients ≥ 18 years old.
3. Performance status 0-2 (Eastern Cooperative Oncology Group classification [ECOG]).

4. Willing to fulfill all follow-up requirements.
5. Medically inoperable primary soft tissue lesion of the lung or patient election not to have surgery.

   (Medically inoperable is defined per the following indicators: post-op predictive FEV1 < 40%; DLCO < 40%; hypoxemia or hypercapnia diabetes with end-organ damage; or severe cerebral, cardiovascular, peripheral vascular disease, or chronic heart disease.)
6. A soft tissue lesion ≤ 2 cm in the outer two-thirds of the lung and not closer than 1 cm to the pleura. Lesion size must be measured with at least 2-dimensional (2D) imaging. Only one lesion meeting the inclusion criteria may be treated during the day of ablation (Visit 2A). However, additional primary disease lesions may be present on the day of ablation.

   (Outer two-thirds of the lung is defined as peripheral beyond the segmental airway, past the segmental bronchi, such that proximal endobronchial soft tissue lesions are avoided; soft tissue lesions should not be contiguous with the pleura.)

7.4 Exclusion Criteria

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

1. Scheduled concurrent procedure for the target soft tissue lesion other than those indicated by the study protocol.
2. Pregnant or breastfeeding.
3. Physical or psychological condition that would impair study participation.
4. Patients with uncorrectable coagulopathy at time of screening.
5. Patient with implantable devices, including pacemakers or other electronic implants.
6. Prior pneumonectomy or bronchiectasis.
7. Severe neuromuscular disease.
8. Platelet count ≤ 50,000/mm^3.
9. ASA (American Society of Anesthesiologists) score of ≥ 4.
10. Inability to tolerate anesthesia.
11. Expected survival less than 6 months.
12. Clinically significant hypertension.
13. 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.)
14. Endobronchial soft tissue lesions proximal to the segmental airways.
15. Convex probe EBUS (CP-EBUS) lymph node sampling that results in a positive diagnosis of malignancy.
16. Imaging findings of active pulmonary infection.

17. The patient was judged unsuitable for study participation by the Investigator for any other reason.

7.5 Prior and Concomitant Therapy

Patients may continue with their current medical care throughout the duration of the study, including medications. All concomitant medications will be recorded on the relevant eCRF page. Do not record components of the anesthesia medications used for the ablation procedure.

7.6 Screening Failures

All patients signing consent who do not meet the inclusion and exclusion criteria or who do not have the ablation procedure initiated, will be recorded as screen failures. The relevant eCRF pages (demographics, reason for screen failure) will be completed for all screen failure patients and thereby the data will be included in the study database.

7.7 Removal of Patients from the Study

In accordance with the current revision of the Declaration of Helsinki and the Code of Federal Regulations, a patient 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 patient (or patient's legally authorized guardian/representative) decide to withdraw from the study, all efforts will be made to collect all AEs they may have experienced. Patients who withdraw or are terminated prior to the ablation procedure will be replaced. [redacted]

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 patient chooses to withdraw early from the study, the eCRF completion page should be completed. When a patient'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.

Ablation:

The Investigator may withdraw a patient during the ablation procedure for any reason, including the following reasons:

1. Inability of Investigator to locate and target the soft tissue lesion.
2. Inability of patient to tolerate the anesthesia.

Death:

When available, the cause of death should be documented.

Lost to follow-up:

All patients should be encouraged to return for protocol required clinic visits for evaluation during the study follow-up period. If a patient is unable to return for a clinic visit or unable to be contacted by telephone, attempts to contact the patient should be documented in the source documents. Only after failing to contact the patient at the final follow-up visit, the patient 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 study at any time. When this occurs, all patients 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 patient 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 patients at a site or for the study as a whole.
- Futility: It is evident that the endpoint cannot be reached given the study design and number of enrolled participants.
- Regulatory body mandate(s).

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

8.0 STUDY PROCEDURES

8.1 Procedure Description(s)

Adult patients with medically inoperable primarily soft tissue lesions of the lung will have a transbronchial microwave ablation [redacted]

[redacted]

[redacted]

Total Radiation Exposure

The total radiation exposure for each patient will be dependent on the number of CTs per patient 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 0.1 mSv to 15 uSv,[6] while the average radiation range for cone beam CT is considerably higher: 19 uSv to 1073 uSv.[7] The total radiation exposure to the patient during the ablation procedure will be captured.

8.1.1 System Overview(s)

[redacted]

[redacted]

8.1.2 Identity of Study Products

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

TEST PRODUCT: NEUWAVE FLEX MICROWAVE ABLATION SYSTEM AND ACCESSORIES

Product Code	**Description**
NWF1US1N	NEUWAVE Flex Microwave Ablation System, 120 Vac DR-000770
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.1.3 Investigational/Study Product Accountability

The NEUWAVE Flex Microwave Ablation System and the microwave ablation probes [redacted] must be stored in conditions according to product labeling and IFU. It is the responsibility of the Principal Investigator to ensure that devices are stored correctly at the site.

The Principal Investigator or responsible person designated by the Principal Investigator 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 Principal Investigator must allow the Study Monitor access to the secured facility where the study devices are stored to check inventory.

The Sponsor will supply the NEUWAVE Flex Microwave Ablation System and the microwave ablation probes to the study sites. Upon receipt, the Investigator will do the following:

- Conduct an inventory.

- Upon confirmation that all materials arrived intact, complete the Packing List for Clinical Supplies included with the shipment. The Sponsor should be contacted immediately if any materials are damaged or missing from the shipment.
- Sign and date the packing list, and promptly return it to the Sponsor.
- 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.

8.2 Visits

Table 1: Schedule of Assessments may be found at the end of Section 1.0 Synopsis.

8.2.1 Visit 1 – Screening

The screening assessments for this visit may occur over several dates within 30 days prior to Visit 2.

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

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

- Patients must be given ample time to review and sign the ICF.
- Collect demographic information (age at time of Visit 1, sex, race, ethnicity).
- Review and collect medical and surgical history, including date of diagnosis of soft tissue lesion under study, radiation history, and smoking status.
- Collect height and body weight for BMI
- Evaluate ECOG performance status.
- Record the American Society of Anesthesiologists (ASA) score, which is a global score that assesses the physical status of patients before surgery.
- Record all prior medications taken within 30 days of Visit 2 and all current medications, including but not limited to chemotherapy, steroids, anti-inflammatories, NSAIDs, hormonal therapy, homeopathic/natural medications, nutritional supplements, and antibiotics.
- Review inclusion/exclusion criteria and determine if the patient is eligible to participate in the study.
- QOL questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung-specific QLQ-LC13. The questionnaires may be administered over the phone, as needed.
- Numeric Pain Rating Scale.
- CT scan of the lung to determine soft tissue lesion details (e.g., size, lesion type, location, shape).
- [redacted] send the scan to the central radiologist for independent review (refer to the Central Radiology Review manual).
- Obtain PFTs, which may include spirometry, diffusion capacity (also called the DLCO [diffusing capacity of the lung for carbon monoxide]), lung volume tests, pulse oximetry, and FeNO tests.
- Laboratory tests. If the following tests (based on the study site's SOC) will be completed within 30 days of Visit 2, then they do not need to be repeated at the

Screening visit:

- CBC (with differentials).
- Coagulation tests (APTT, INR, PT, PTA, PTT).
- Serum pregnancy test, for women of childbearing potential only.
- Any genetic markers relevant to the lesion, if done per SOC.

8.2.2 Visit 2 – Ablation Procedure Through Discharge (Visit 2B)

[redacted]

On the day of ablation, cone beam CT scans will be done at the timepoints listed in the section below.

Visit 2A: Intraoperative (Ablation)

Data collected before and during the procedure:

- Administer antibiotics prior to the ablation procedure.
  [redacted]
- Measure and record the size of the lesion to confirm inclusion criteria (lesion must be ≤ 2 cm).
- Prior to ablation, confirm that the patient still meets inclusion and exclusion criteria (tests not needed to be repeated).
- Collect height and body weight for BMI, and evaluate ECOG performance status (prior to ablation).
- Record all concomitant medications, including but not limited to chemotherapy, steroids, anti-inflammatories, NSAIDs, hormonal therapy, homeopathic /natural medications, nutritional supplements, and antibiotics. Do not record components of the anesthesia medications used for the ablation procedure.
- Record all concomitant procedures.
- QOL questionnaires EORTC QLQ-C30 and the lung-specific QLQ-LC13 (prior to ablation). The questionnaires may be administered over the phone, as needed.
- Numeric Pain Rating Scale (prior to ablation).
  [redacted]

[redacted]

- User Experience Survey answered by the treating physician post-ablation (available as a separate document).
- Evaluate technical success, defined as ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin). [redacted]
- Radiation exposure from the CT scans.
- Record any AEs/SAEs that occur from the start of the ablation.

Visit 2B: Discharge

After the ablation procedure, the patient will be observed for up to 23 hours and afterwards discharged from the study site (except in cases where the Investigator deems it is necessary for the patient to remain hospitalized). During that 23-hour period, the following assessments will occur:

- Record all concomitant medications.
- Record all concomitant procedures.
- QOL questionnaires EORTC QLQ-C30 and the lung-specific QLQ-LC13. The questionnaires may be administered over the phone, as needed.
- Numeric Pain Rating Scale.
- Length of hospital stay, measured from post-ablation to discharge.

- All AEs/SAEs.
- De-identified UB-04 data, if allowed, to be provided to the Sponsor by the site.

8.2.3 Visit 3 – 30-day Follow-up

One month (approximately 30 days ± 7 days) after the ablation procedure, the patient will visit the study site and the following assessments will occur:

- Record all concomitant medications.
- All concomitant procedures.
- QOL questionnaires EORTC QLQ-C30 and the lung-specific QLQ-LC13. The questionnaires may be administered over the phone, as needed.
- Numeric Pain Rating Scale.
- Collect height and body weight for BMI, and evaluate ECOG performance status.
- CT scan to determine soft tissue lesion details (e.g., size, lesion type, location, shape). [redacted]
- Laboratory tests, as follows:
  - CBC (with differentials).
  - Coagulation tests (APTT, INR, PT, PTA, PTT).
- Technique efficacy, defined as ablation of the target lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin). [redacted]
- Record readmission to any hospital for any reason within 30 days of the ablation. The Investigator will assess the reason for the admission and capture the reason in the clinical database.
- All AEs/SAEs.

8.2.4 Visit 4 – 6-month Follow-up

Visit 4 occurs 6 months (± 1 month) after the first ablation procedure (Visit 2A). The patient must visit the study site for the following assessments:

- Record all concomitant medications.
- All concomitant procedures.
- QOL questionnaires EORTC QLQ-C30 and the lung-specific QLQ-LC13. The questionnaires may be administered over the phone, as needed.

- Collect height and body weight for BMI, and evaluate ECOG performance status.
- CT scan to determine soft tissue lesion details (e.g., size, lesion type, location, shape). [redacted]
- Obtain PFTs (spirometry, diffusion capacity (DLCO), lung volume tests, 6-minute walk or pulse oximetry, and FeNO tests).
- Laboratory tests, as follows:
    a. Complete blood count (CBC; with differentials).
    b. Coagulation tests (APTT, INR, PT, PTA, PTT).
- Record the number of successful repeat ablations, if applicable.
- All AEs/SAEs.

8.2.5 Visit 5 – 12-month Follow-up / End-of-Study

Approximately 12 months (± 1 month) after the first ablation procedure is Visit 5, the end-of-study visit. At this final visit of the study, the patient will visit the study site where the following assessments will occur:

- Record all concomitant medications.
- All concomitant procedures.
- QOL questionnaire (EORTC QLQ-C30) and the lung-specific QLQ-LC13. The questionnaires may be administered over the phone, as needed.
- Collect height and body weight for BMI, and evaluate ECOG performance status.
- CT scan of the lung to determine soft tissue lesion details (e.g., size, lesion type, location, shape). [redacted]
- Obtain PFTs (spirometry, diffusion capacity (DLCO), lung volume tests, 6-minute walk or pulse oximetry, and FeNO tests).
- Laboratory tests, as follows:
    a. Complete blood count (CBC with differentials).
    b. Coagulation tests (APTT, INR, PT, PTA, PTT).
- Record the number of successful repeat ablations, if applicable.
- All AEs/SAEs.
- Record date of study completion.

8.2.6 Unscheduled Visits

The following data will be collected during each unscheduled visit:

- Reason for the unscheduled visit.
- AEs/SAEs, if applicable.
- Any update to concomitant medications and procedures.

9.0 DATA MANAGEMENT AND INTEGRITY

9.1 Data Completion and Record Keeping

Source Documents

Source documents are documents on which information regarding patients is first recorded, including printed, optical, or electronic documents. Investigator patient files or hospital records generally are the basis of source document information. This includes, but is not limited to, the following: original patient 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.

[redacted]

All cone beam CT scans (taken during the ablation procedure) and all conventional CT scans (taken during the post-ablation follow-up visits) should be sent in DICOM format (where possible) [redacted]

[redacted]

[redacted]

[redacted]

Source documents must be retained by the Investigator as part of the patient'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, patient 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 (Medidata Rave, 350 Hudson Street, 9th Floor, New York, NY 10014 United States; telephone: 212-918-1800; Fax: 212-918- 1818; toll-free: 877-511-4200). This system was designed and is developed and maintained by Medidata, Inc. 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 patient 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 Medidata Rave website to assist in the collection and entry of source data into the electronic casebook.

A 24/7/365 Help Desk Support line (telephone: 973-659-6780; fax: 973-954-5621; toll free: 866-633-4328; Email: helpdesk@mdsol.com) 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 Principal Investigator (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 patient. The patient's unique study ID number will be visible on each eCRF. At no time, should the patient 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 patient'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 within Medidata Rave.

Data Privacy

The collection, use, and disclosure of all personal data, including patient 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 patient. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of patient 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 patient.

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 patient'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 patients 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.

9.2 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) will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

9.3 Data Quality Assurance

A protocol deviation is any noncompliance with the study protocol, Good Clinical Practice, or protocol-specific requirements. A deviation (any activity conducted outside the parameters established by the study 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 as required by the IRB procedures.

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 on-site monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

Any deviations from the protocol or procedures should be recorded in the source documents.

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

Investigator Training

Prior to screening patients 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.

Monitoring

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

- The rights and well-being of the patients 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 (i.e., monitoring plan) specified by the Sponsor for monitoring this study as characterized in the monitoring plan.

9.4 Protocol Deviations

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate sites, the 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 on-site monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

10.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

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 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 patients, mean, standard deviation, median, minimum, and maximum.

10.2 Study Design

This is a multicenter, single-arm study.

10.3 Treatment Assignment

This is a single-arm study where all enrolled patients will receive the same treatment: microwave ablation performed with the flexible probe using the NEUWAVE Flex Microwave Ablation System and Accessories. 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

The primary objective of this study is to evaluate the NEUWAVE Flex Microwave Ablation System and Accessories in transbronchial ablation procedures for adult patients with medically inoperable primary soft tissue lesion that are ≤ 2 cm, located in the outer two-thirds of the lung and not closer than 1 cm to the pleura, at Visit 3, which is 30 days ± 7 days after the first ablation procedure, based on the following:

a) Device user experience
b) Technical success
c) Technique efficacy.

The data for the evaluation of device user experience will come from the User Experience Survey, which will be completed by the treating physician following each ablation procedure throughout the study, when applicable.

Primary endpoints for technical success and technique efficacy are defined in Section 6.0, above.

The study will be descriptive in nature and thus no hypotheses for any of the primary endpoints are specified levels of significance.

10.6 Levels of Significance

No levels of significance are specified because no hypotheses are planned to be tested.

10.7 Analysis Sets

The primary analysis of safety and effectiveness endpoints will be performed on the Full Analysis Set, defined as all patients who are enrolled in the study and receive ablation through the flexible probe. A Per Protocol analysis set will be defined as all patients who had 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

No formal hypotheses are being tested in this study and hence a target sample size of 40 patients [redacted] is deemed adequate for a preliminary investigation of the feasibility of this procedure, as well as for providing sufficient information for appropriately sizing a subsequent study.

[redacted]

10.9 Analyses to be Conducted

Analyses described below will be performed on the pooled set of 40 patients [redacted]

Disposition of Study Patients

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

Demographic and Baseline Characteristics

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

Primary and Secondary Endpoint Analyses

Device user experience feedback will be collected from the treating physician who will complete the User Experience Survey following each ablation procedure. The questionnaire will focus on procedure workflow and the user's assessment on ease/difficulty of using the device. Summary statistics will be provided for each question.

The number and percentage of patients achieving technical success will be summarized and a 95% confidence interval will be estimated. Technique efficacy, as well as primary and secondary efficacy rates and hospital readmission rates, will be summarized in a similar manner. Local soft tissue lesion recurrence rates will be estimated using the Kaplan-Meier method and 95% confidence intervals will be provided.

The number and percentage of patients experiencing AEs from the start of ablation (Visit 2A) to Visit 3 (the first post-ablation visit) will be summarized by MedDRA preferred term and system organ class. A similar summary will also be provided for device related and procedure related, and all SAEs. Ninety-five percent confidence intervals may be provided for pre-specified adverse events of interest [redacted]

[redacted]

Similar summaries will also be provided for the entire observation period from the ablation procedure date through 1 year of follow-up.

The EORTC QOL questionnaires and 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 interim analyses, whose intent would be to stop the study early or to modify the study design. Two analysis timepoints are planned. The first analysis will occur after all patients within a treatment group (interventional pulmonologist or thoracic surgeon) complete Visit 3 (30 days ± 7 days after the first ablation procedure). The analysis will provide a summary of the User Experience Survey, technical success, technique efficacy, and safety through Visit 3. When the second group completes this timepoint, results will be summarized for that group and subsequently in total. The second analysis timepoint will be at the completion of the study.

Ongoing Review

[redacted]

The Sponsor will also review complications periodically, as per the Safety Management Plan. [redacted]

[redacted]

A report of death will stop enrollment and require an investigation to determine if the death is related to the ablation procedure. If the death is deemed not related to the ablation procedure the study may resume enrollment.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be appointed by the Sponsor to review, on a regular basis, safety data from the study. The DSMB will advise the Sponsor regarding the continuing safety of patients and those yet to be recruited to the study. Based on accumulating 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 40 patients, 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.

Analysis of Safety

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

Handling of Dropouts or Missing Data

All analyses will be performed only on patients undergoing ablation with the flexible probe and only observed data will be analyzed. There will be no imputation of missing data for any parameters or for early terminated patients.

Multicenter Studies

No adjustment for center is planned in the statistical analysis. However, center specific analyses may be conducted pending within-center sample size to understand the effect that surgeon techniques and site's SOC may have on the overall results.

[redacted]

11.0 RISKS AND BENEFITS OF THE STUDY

This study may or may not provide any benefits to the patient. However, the data collected throughout the study may help to assess the efficacy and safety of a new treatment technique: transbronchial microwave ablation of soft tissue lesions of the lung. As described in the Introduction, retrospective studies of patients who underwent percutaneous microwave ablation of the lung as far back as 2003 have provided data that the percutaneous route of treatment has been safe and effective. Transbronchial microwave ablation of soft tissue lesions represents a new approach that has not been routinely used in clinical practice, so there may be some unforeseeable and unknown risks associated with this technique in this study.

12.0 ADVERSE EVENTS

12.1 Definitions

Adverse Event

For this study, an adverse event is defined as any undesirable clinical occurrence in a patient. All AEs, whether attributable to the device/procedure or not, are to be recorded in the eCRF and reported to the Sponsor.

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

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:

- Life-threatening: The patient was at imminent risk of dying at the time of the adverse event.
- Permanent Impairment: An AE that resulted in permanent impairment of a body function or permanent damage to a body structure.
- Necessitated Intervention: An AE that resulted in a condition that necessitated medical or surgical intervention to preclude permanent impairment of a body function or damage to a body structure.
- Required in-patient or prolonged hospitalization.
- A persistent or significant disability or incapacity.
- Resulted in death: An AE that resulted in the patient's death

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 SAE. The only exception is "Sudden Death" when the cause is unknown.

3. Planned hospitalization for a pre-existing condition is not considered an SAE.

4. A procedure required by the protocol is not considered an SAE, unless the patient experiences a serious deterioration in health or hospitalization is prolonged.

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

Severity of Adverse Events

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE.

The severity of each AE will be determined via the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE may be accessed here: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Also, the following guideline should be used to determine the severity of each AE:

- **MILD:** Awareness of signs or symptoms, but does not interfere with the patient's usual activity, or is a transient event that resolves without treatment and with no sequelae.
- **MODERATE:** A sign or symptom, which interferes with the patient's usual activity.
- **SEVERE:** Incapacity with inability to do work or usual activities.

Relationship of Adverse Events

It is the Investigator's responsibility to assess the relationship between all AEs and the study procedure.

The following guidelines should be used in determining the relationship of an AE to a device, study procedure, or other causality:

Not related	Temporal sequence between device usage and the event is such that the relationship is unlikely.
Unlikely related	Temporal sequence between device usage and the event is such that the relationship is not unlikely or the subject's condition or concomitant therapy could have caused the AE.
Possibly related	Temporal sequence is relevant or the event abates upon device usage completion or the event cannot be reasonably explained by the patient's condition.
Probably related	Temporal sequence is relevant and the event abates upon product device usage or reappearance of the event on repeat device usage (re-challenge).
Causal relationship	Temporal sequence between device usage and the event is such that the relationship is unlikely.

12.2 Reporting Adverse Events

The Investigator is required to report all AEs experienced by the patient from the start of the ablation procedure (Visit 2A) until the patient completes Visit 5 (1 year after the first ablation procedure) or withdraws early (prior to Visit 5) to the Sponsor within 14 days of become aware of the AEs. All AEs (both serious and non-serious) must be reported in the AE eCRF. The Investigator will evaluate the severity of the event and its relatedness to the study device or procedure.

Any necessary medical management of the event will be recorded in the patient's medical record/source document. All AEs must be followed until resolution or until they become stable.

The Investigator will record all AEs (both serious and non-serious) in the source documents. CTC (Common Terminology Criteria) should be used when recording AEs. In addition, the following information should be recorded:

- Onset date
- Resolution date or date of death
- Severity of the event using CTCAE
- Action taken
- Event status (ongoing at study end or resolved)
- Relationship of AE to the ablation device used in the study
- Relationship of AE to the study procedure
- Indication of seriousness.

Data related to SAEs will be collected until event resolution, or until the event is considered stable, or until all attempts to determine the resolution of the event are exhausted. All AEs that are unresolved at study completion (or early termination) will be recorded as ongoing at study end.

Reporting Serious and Non-Serious Adverse Events to the Sponsor

The study site must report all SAEs, whether they are related to the device or procedure, to the Sponsor as soon as possible, but no later 72 hours of becoming aware of the SAE. The study site will report the SAE by entering the event into the EDC system via the Adverse Event eCRF, which will trigger an automated email to the Sponsor. Additional information, including the Investigator's assessment, may be added to the eCRF later; however, the study site must complete the AE eCRF within 72 hours of becoming aware of the SAE. If the Sponsor requires supporting documentation or other information, the Sponsor will contact the study site.

In the event of death, the Investigator must report all available information to the Sponsor.

The report of an 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 to the reviewing IRB/EC, per their IRB/EC procedures.

Regarding non-serious AEs, the study site is expected to complete the Adverse Event eCRF within 14 days of becoming aware of the event. The Investigator must assess expectedness, which also will be recorded in the AE eCRF. Supporting documentation may be requested, as needed.

13.0 PRODUCT COMPLAINTS

13.1 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 after it is released for distribution (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. Device malfunction (the failure of a device to perform as intended for this study).

13.2 Reporting Product Complaints

All product complaints related to devices in the procedure shall be documented throughout the clinical investigation.

The study site must report product complaints related to a device manufactured by NeuWave Medical, Inc., in a timely manner, but no later than 24 hours of becoming aware of the event.

When any representative of the Sponsor becomes aware of a product complaint, the Sponsor representative must notify the Sponsor's Product Complaint Team within 24 hours of becoming aware of the event.

The Product Complaint Form must be emailed to the Sponsor Customer Complaint team [redacted]

One copy of the processed form should be kept on-site and the device should be retained. Sponsor representatives will organize collection of the device for evaluation, as needed.

14.0 PUBLICATION PLAN

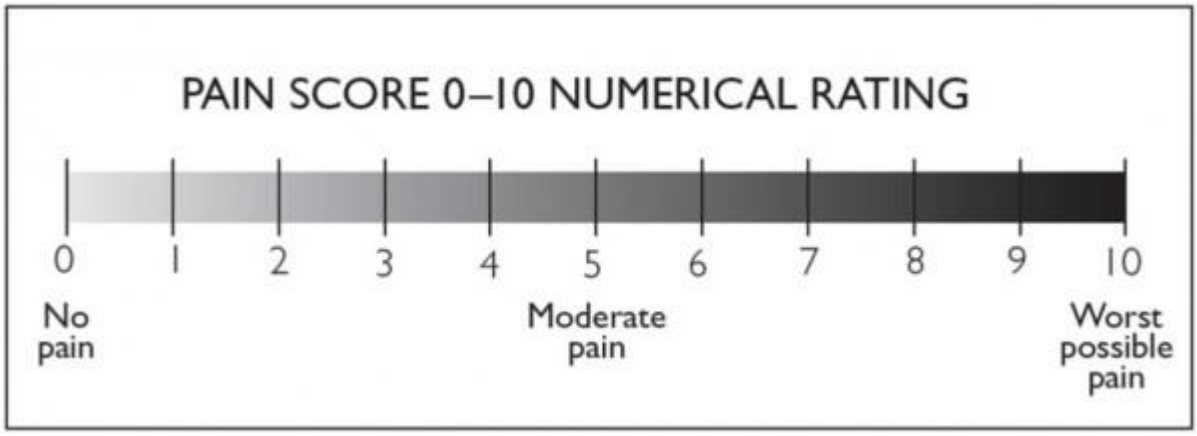
Publication and authorship policies should be determined and aligned with the clinical study agreement executed between operating company and each clinical site. Publication of the results of this study will be governed by J&J publication policies, including current and applicable Medical Device Publication 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.

15.0 APPENDICES

APPENDIX 1: Numeric Pain Rating Scale

The Numeric Pain Rating Scale (NPRS) can be administered verbally (therefore also by telephone) or graphically for self-completion. As mentioned above, the respondent is asked to indicate the numeric value on the segmented scale that best describes their pain intensity.



APPENDIX 2: SPONSOR CONTACT INFORMATION

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

16.0 REFERENCE LIST

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