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A Study to Evaluate the Safety and Effectiveness of Microwave Ablation in Patients with Hepatocellular Carcinoma in Korea

Protocol Number: NEU_2017_01

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INVESTIGATOR SIGNATURE

I have read and understood this protocol, and agree to:

- Conduct this clinical study in accordance with the design and specific provisions outlined herein;
- Ensure the clinical study is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations, the Declaration of Helsinki, the signed Clinical Trial Agreement with Sponsor, and with the protocol outlined herein;
- Make reasonable effort to complete the clinical study within the time period designated by the Sponsor;
- Maintain the confidentiality of all information received or developed in connection with this protocol;
- Provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of the clinical study, and will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the clinical study;
- Fulfill the requirements of my Institutional Review Board (IRB), or other oversight committee, to ensure complete and continual oversight of this clinical study;
- Use an Informed Consent Document approved by the Sponsor and my reviewing IRB and ensure that the requirements for obtaining informed consent are met;
- Report any serious adverse events, device related adverse events, or procedure related adverse events, or Ethicon Product Complaints to the Sponsor as soon as possible, but no later than 24 hours after becoming aware of the event, and provide follow-up information no later than ten days after becoming aware of the event, and comply with all adverse event reporting requirements of my reviewing IRB;
- Permit the Sponsor, its authorized representatives, my reviewing IRB, and any regulatory authority/body access to all records relating to the clinical study;
- Adhere to the publication policy, as stated in the Clinical Trial Agreement, for data collected during this clinical study;
- Be responsible for the initial and continuing review and approval of the clinical study;
- Promptly report to my reviewing IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others;
- Not make any changes in the research without Sponsor and my reviewing IRB approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects; and
- Comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the Sponsor and government agencies.

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

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1.0 RESPONSIBLE PARTIES INVOLVED IN THE STUDY

A list of all responsible parties, such as medical monitors, and contract research organizations, who are involved in the operations of the study is filed in the Sponsor's Trial Master File. The names of the individuals and corresponding phone numbers who should be contacted regarding the conduct of the study, adverse events, safety issues, and complaints are provided in the Site Investigator File.

2.0 SYNOPSIS

Title:	**A Study to Evaluate the Safety and Effectiveness of Microwave Ablation in Patients with Hepatocellular Carcinoma in Korea**
Protocol Number:	NEU_2017_01
Products:	Neuwave Medical's Certus 140™ Ablation System used with Certus LK Probes (LK15, LK15XT, LK20 and LK20XT) or PR Probes (PR15, PR20, PR15XT and PR20XT). These are collectively described as "study devices."
Regulatory Classification:	Registered Devices used in a clinical trial • Certus LK Probes (LK15, LK15XT, LK20, or LK20XT) or PR Probes (PR15, PR20, PR15XT, or PR20XT) (Class 2) • Neuwave Medical's Certus 140™ Ablation System (Class 3)
Control:	N/A
Device Indication:	The NeuWave Medical's Certus 140™ 2.45 GHz Ablation System and Accessories are indicated for the ablation (coagulation) of soft tissue in percutaneous, open surgical, and in conjunction with laparoscopic surgical settings. Certus 140™ Ablation Probes are designed for use only with the Certus 140™ 2.45 GHz Ablation System. The Certus 140™ 2.45 GHz Ablation System is not indicated for use in cardiac or endometrial procedures. The study devices will be utilized as described in the IFU. In this study, the study devices will only be used for the ablation or coagulation of liver tissue in percutaneous settings.

Objective(s):	To evaluate the outcomes of microwave ablation of patients with hepatocellular carcinoma (HCC) of ≥ 2 cm and up to 5 cm.
	
	• <u>Primary Endpoint:</u>
	Technical Success, defined as complete tumor ablation with adequate or insufficient ablation margin, based on contrast-enhanced MRI and CT scans immediately following the ablation procedure.
	
	• <u>Secondary Endpoints:</u>
	  • Primary Technique Efficacy, defined as complete tumor ablation with adequate or insufficient ablation margin, based on contrast-enhanced MRI and CT scans follow-up at 1 month after the ablation procedure;
	  • Local tumor progression (LTP) rate, evaluated at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months after the ablation of the index tumor;

	• Primary efficacy rate, defined as the percentage of target tumors successfully eradicated following the ablation procedure; • Secondary efficacy rate, defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression; • Progression free survival and overall survival rates at 36 months after the ablation procedure; • Rate of adverse events reported through 3 months and cumulatively through study completion; • Quality of Life, as measured by VAS pain score, EORTC QLQ-C30 and EORTC QLQ-HCC18, before the ablation procedure and at each post-ablation visit; • Health economics associated with the ablation procedure: complete procedure time, ablation time, no. of ablations, length of stay, no. and types of probes used.
Study Design:	This prospective, single-arm single center study will provide clinical data using Neuwave Medical's Certus 140™ 2.45GHz Ablation System used with Certus LK Probes (LK15, LK15XT, LK20, and LK20XT) or PR Probes (PR15, PR20, PR15XT, and PR20XT) (study devices). Individuals who undergo microwave ablation of liver tumors in accordance with their institution's standard of care (SOC) for ablation, and who meet study entry criteria, may be enrolled. The enrollment for the study will continue until 30 eligible subjects complete the 3-month visit after ablation (Visit 4) for the primary effectiveness and safety analysis. The subjects will be followed for up to 36 months after the ablation procedure for safety and ablation outcomes.
Number of Sites:	One (1) site in Korea
Sample Size:	Total planned: 30 subjects who complete 3-month visit after ablation (Visit 4):
Diagnosis/Criteria for Inclusion:	1. Confirmed hepatocellular carcinoma, tumor ≥ 2 cm and up to 5 cm, single location, BCLC Stage A based on imaging (CT Scan or MRI or ultrasound) and biopsy confirmation in accordance with their institution's standard of care (SOC) procedure; 2. Primary hepatocellular carcinoma or recurrent hepatocellular carcinoma which was previously treated with ablation or surgical resection only; 3. Scheduled for microwave ablation of the liver; 4. Performance status 0-2 (Eastern Cooperative Oncology Group classification); 5. Functional hepatic reserve based on the Child-Pugh score (Class A or B); 6. ASA score $\leq$ 3; 7. Given voluntary, written informed consent to participate in this study and has authorized the transfer of his/her information to the Sponsor, and willing to comply with study-related evaluation and treatment schedule; and 8. At least 19 years of age.

Diagnosis/Criteria for Exclusion:	1. Active (subject currently receiving systemic treatment) bacterial infection or fungal infection; 2. Systemic administration (intravenous or oral) of steroids, including herbal supplements that contain steroids, within 30 days prior to the study procedure; 3. Chemotherapy or radiation therapy for hepatocellular carcinoma may not be performed for 30 days prior to the study procedure; 4. Subject with implantable pacemakers or other electronic implants; 5. Planned/ scheduled liver surgery. 6. Subject with a platelet count of less than 50,000/$mm^{3;}$ 7. Subject with an INR greater than 1.5; 8. Subject with renal failure on renal dialysis; 9. Scheduled concurrent procedure other than microwave ablation in the liver; 10. Pregnant or breastfeeding; 11. Physical or psychological condition which would impair study participation; 12. Participation in any other clinical study concurrently or within the last 3 months; 13. The subject is judged unsuitable for study participation by the Investigator for any other reason; or 14. Unable or unwilling to attend follow-up visits and examinations.
Study Duration:	Planned Recruitment Period: 9-12 months Follow-up Period: up to 36 months
Safety:	All adverse events (AEs) will be recorded and reported appropriately throughout the study.
Statistical Methods:	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. Confidence intervals will also be provided for procedure-related variables. The number and percentage of subjects achieving Technical Success will be summarized and an exact 95% confidence interval will be estimated. A similar summary will be provided for Primary Technique Efficacy, as well as for the primary and secondary efficacy rates as previously defined. Local tumor progression rates at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months will be estimated using the Kaplan-Meier method and 95% confidence intervals will be provided. The number and percentage of subjects experiencing adverse events (AEs) will be summarized at the preferred term level using the Society of Interventional Radiology (SIR) clinical practice guidelines for event categorization. Two analyses of study data are planned. The first will occur after 30 subjects have completed the 3-month visit and is intended to provide an initial estimate of device effectiveness for Technical Success as well as to summarize the peri-operative out to 3-month post-operative safety

	profile of subjects undergoing microwave ablation. There are no plans to use the results of the first analysis for the purpose of stopping the study early. The second analysis will occur after all subjects have completed study participation.

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Table 1: Schedule of Events

Visit No.	Visit 1:	Visit 2A	Visit 2B	Visit 2C	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	USV
Visit	**Screening**	**Pre-Ablation**	**Ablation**	**Post-Ablation**	**1 month**	**3 months**	**6 months**	**9 months**	**1 year**	**18 months**	**2 years**	**30 months**	**3 years**	**Unscheduled Visit[9]**
Interval Windows	Within 5 weeks before ablation	-2 to 0 days	Day 0= Ablation of index tumor	0 to 4 days	1 month (+/- 14 days) after ablation	3 months (+/-28days) after ablation	6 months (+/-28 days) after ablation	9 months (+/-28 days) after ablation	12 months (+/-28 days) after ablation	18 months (+/-28 days) after ablation	24 months (+/-28 days) after ablation	30 months (+/-56 days) after ablation	36 months (+/-28 days) after ablation	NA
Study Activity														
Informed Consent	X													
Demographic Information	X													
Medical/ Surgical History	X	X												
Inclusion/ Exclusion Criteria	X	X												
VAS Pain Score		X		X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30		X			X	X	X	X	X	X	X	X	X	
EORTC QLQ-HCC18		X			X	X	X	X	X	X	X	X	X	
CT Scan (Liver)[1]	X		X	X	X	X	X	X	X	X	X	X	X	
MRI (Liver)[2]			X	X	X	O[2]	O[2]	O[2]	O[2]	O[2]	O[2]	O[2]	O[2]	
Ultrasound (Liver)[3]	X		X											
Coagulation Test[4.1]	X	X		X	X	X	X	X	X	X	X	X	X	
Liver Function Test[4.2]	X	X		X	X	X	X	X	X	X	X	X	X	
Renal Function Test[4.3]	X	X		X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC)[4.4]	X	X		X	X	X	X	X	X	X	X	X	X	
Alpha-fetoprotein (AFP)[4]	X			X	X	X	X	X	X	X	X	X	X	
PIVKA-II[4]	X	X		X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[4.5]	X													
Tumor Size, Type and Location	X		X											
BCLC Staging	X		X											
ECOG Performance Status	X	X			X	X	X	X	X	X	X	X	X	
Child-Pugh Score	X													
ASA Score		X												
Procedure Details[6]			X											
Device Accountability			X											

Visit No.	Visit 1:	Visit 2A	Visit 2B	Visit 2C	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	USV
Visit	**Screening**	**Pre-Ablation**	**Ablation**	**Post-Ablation**	**1 month**	**3 months**	**6 months**	**9 months**	**1 year**	**18 months**	**2 years**	**30 months**	**3 years**	**Unscheduled Visit[9]**
Interval Windows	Within 5 weeks before ablation	-2 to 0 days	Day 0= Ablation of index tumor	0 to 4 days	1 month (+/- 14 days) after ablation	3 months (+/-28days) after ablation	6 months (+/-28 days) after ablation	9 months (+/-28 days) after ablation	12 months (+/-28 days) after ablation	18 months (+/-28 days) after ablation	24 months (+/-28 days) after ablation	30 months (+/-56 days) after ablation	36 months (+/-28 days) after ablation	NA
Study Activity														
Length of Hospital Stay		X		X										
Complete Tumor Ablation Evaluation			X		X									
LTP Evaluation					X	X	X	X	X	X	X	X	X	
Follow-up Post-ablation Treatment[7]					X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Relevant Concomitant Procedures				X	X	X	X	X	X	X	X	X	X	X
Adverse Event and SAEs[8]			X	X	X	X	X	X	X	X	X	X	X	X

Notes:

1. CT Scan of the liver: For Visit 1, the CT Scan must be performed within 37 days of the visit and the subject does not need to repeat a CT scan of the liver, if the liver CT scan based on SOC was done within 37 days of Visit 1. For Visit 2B/2C, the CT Scan will be done up to 4 days after the completion of the ablation procedure for all subjects, and CT Scan may also be used to guide the ablation procedure for some subjects. For the follow-up Visits 3 to 11, the CT Scan may be done within 14 days prior to the visit.
2. MRI of the liver: For Visit 2B/2C, the MRI will be done up to 4 days following the completion of the ablation procedure for all subjects. For Visit 3, the MRI may be done within 14 days prior to the visit. After Visit 3, a MRI may be done once per year of follow-up, if applicable, depending on each subject's condition and based on the clinical judgement of the Investigator (hence, O = optional).
3. Ultrasound of the liver: For Visit 1, the planning ultrasound will be done on the day of the visit or up to 7 days prior. For Visit 2B, ultrasound is used to guide the ablation procedure.
4. For Visit 1, the laboratory tests must be performed within 37 days of the visit and the subject does not need to repeat the laboratory test(s), if the laboratory test(s) based on SOC was/ were done within 37 days of Visit 1. For the follow-up Visits 3 to 11, the laboratory tests will be done within 14 days prior to the visit.
   4.1. Coagulation Test: Includes PT, APTT, and INR
   4.2. Liver Function Test: Includes AST, ALT, GGT, albumin, indirect, direct and total bilirubin, and total protein.
   4.3. Renal Function Test: Includes BUN, Creatinine and electrolytes (sodium, potassium and chloride).
   4.4. Complete Blood Count (CBC): Includes differential cell count and platelet count.
5. Pregnancy test: For women of child bearing potential only.
6. Procedure Details: Includes complete procedure time, ablation time, anatomical location of ablation, procedure performed, no. of probe placement attempts per probe, no. of ablations, and ablation maximum power and time settings. Some of the ablation procedure details will be provided to the site via a report generated from NeuWave Medical's Call Home Database. The study site will review the report and enter the procedure details into the clinical database, as applicable.
7. Follow-up Post-Ablation Treatment: If applicable.

8. Adverse Event and SAEs: Subjects will be assessed for safety from day of ablation through the 3-year follow-up. All AEs and SAEs will be reported from the day of the ablation up to 3 months after the ablation procedure. Expected serious adverse device effects (SADE), unexpected serious adverse device effects (USADE), life-threatening events, or events that result in death, and all SAEs with definite, possible, probable or unknown relationship to the study device or study procedure, will be reported from day of the ablation through the 3-year follow-up.
9. Unscheduled visits are only for those which are procedure, device or disease related.

NOTE:

- Subjects who have recurred at the target lesion or progressed with a new lesion following the first ablation, and are treated with any treatment post progression will be followed every 6 months (+/-28 days) from the day of the first ablation as a clinic visit or, if clinic visit is not possible, a phone contact visit (if a clinic visit is not possible). This will be called a "Reduced Follow-Up Schedule."

3.0 GLOSSARY

Table 2. Acronyms/ Abbreviations

Acronyms/ Abbreviations	Terms
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AFP	Alpha-fetoprotein
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
APTT	Activated Partial Thromboplastin Time
ASADE	Anticipated Serious Adverse Device Effect
ASA	American Society of Anesthesiologists
BCLC	Barcelona Clinic Liver Cancer
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESC	Ethicon Surgical Care
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma- Glutamyl Transferase
HCC	Hepatocellular Carcinoma
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LOS	Length of Stay
MAUDE	Manufacturer and Facility User Device Experience
MDR	Medical Device Report
MDVR	Medical Device Vigilance Report
MM	Medical Monitor
MPR	Medical Device Problem Report
MRI	Magnetic Resonance Imaging

Acronyms/ Abbreviations	Terms
MWA	Microwave Ablation
OR	Operating Room
PI	Principal Investigator
PIVKA-II	Prothrombin Induced by Vitamin K Absence or Antagonist-II
PDM	Power Distribution Module
PT	Prothrombin Time
RF	Radiofrequency
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIR	Society of Interventional Radiology
SOC	Standard of Care
USV	Unscheduled Visit

4.0 INTRODUCTION

The Neuwave Medical Certus 140™ 2.45 GHz Ablation System and Accessories consist of Software version 2.1.X and the accessories CertusPR, CertusLK, CertusLN and CertusSR ablation probes and CertuSurgGT Surgical Tool. A dual probe clip and several accessories designed to allow for the mechanical interfacing of the Power Distribution Module (PDM) to a variety of vendors' CT Tables are also available. These accessories are ease-of-use and convenience accessories that do not impact the clinical functionality of the system and thus are not described in detail.

The Certus 140™ 2.45 GHz Ablation System and Accessories form a Microwave Ablation System which is intended to ablate/coagulate soft tissue. The Certus 140™ Microwave Ablation System and Accessories are a general purpose thermal ablation tools used by physicians to ablate soft tissue lesions in a wide variety of tissue and disease states. The Certus 140™ 2.45 GHz Ablation System and Accessories are currently cleared by the United States (US) Food and Drug Administration (FDA) and has been in clinical use since 2011 in the United States. The most common applications by clinicians have been the ablation of liver, kidney and lung lesions. Additional, but less common uses have been the ablation of soft tissue lesions in bone and nerve ablation.

This study is a single arm prospective trial to evaluate the safety and effectiveness of microwave ablation in patients with hepatocellular carcinoma in Korea of at least 19 years of age. Pre-clinical and clinical data has shown that microwave ablation is safe and effective in liver tumors with low complication rates, high rates of technical success, lower rates of local tumor progression and promising disease-free and overall survival rates than have historically been reported for radiofrequency (RF).

The Certus 140™ Microwave Ablation System and Accessories is contraindicated for:

- Use in cardiac procedures
- Pregnant patients – *potential risks to patient and/or fetus have not been established*
- Patients with implantable pacemakers or other electronic implants. *Implanted electronic devices may be adversely affected by microwave power*
- Use on the central nervous system
- Endometrial applications

Refer to the Certus 140™ Microwave Ablation System and Accessories accompanying documents for a list of Warnings and Cautions.

All hazards associated with the use of the Certus 140 have been identified and appropriately mitigated. Design considerations were taken to reduce the risks associated with existing microwave ablation systems, including improved system usability and cable management.

The Certus 140 does use a CO_2 cooling system where all other microwave systems use sterile water, but the risks associated with this cooling system do not differ from the risks inherent in cryogenic ablation systems, also widely accepted in clinical use. Thus, the Certus 140 does not introduce new hazards or intended uses.

The risk/ benefit profile of the Certus 140™ Microwave Ablation System and Accessories are acceptable for the intended use of the ablation/ coagulation of soft tissue relative to other medical alternatives.

The information provided by the User Manual and Instructions for Use (IFU) are adequate to describe the use, risks and benefits of the devices.

4.1 LIVER CANCER REVIEW

Liver cancer represents 6% and 9% of the global cancer incidence and mortality burden, respectively. With an estimated 746,000 deaths in 2012, liver cancer is the second most common cause of death from cancer worldwide and it is the sixth most common cancer worldwide. According to the Korean Ministry of Health and Welfare statistics[1,2], in 2014, the rate of liver cancer is 7.5% and is ranked 6th among all cancers, specifically the 4th most common cancer for males (10.7%) and the 6th most common cancer for females (4.0%). Based on 2013 data in Korea[3], the crude mortality rate of liver cancer per 100,000 is 22.2, just ranked 2nd after lung cancer. The relative survival rate of liver cancer from 2010 to 2014 is 32.8%, with an increasing trend since 1993[1].

Hepatocellular carcinoma (HCC) is the most common type of liver cancer in Asia where chronic hepatitis B virus and hepatitis C virus infections are the major causes of liver cancer. Other causes include toxic injury, typically initiated by ingestion of aflatoxin or consumption of alcohol. Incidence rates of hepatocellular carcinoma in men are more than twice those in women as men have higher rates of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, and chronic alcohol consumption with possible hormonal influences on modulation of hepatocarcinogenesis.

Due to the heterogeneous epidemiology and clinical presentation of HCC worldwide, there are no universally accepted consensus practice guidelines for HCC. In Asia, there are regional and national guidelines based on the experience of the consensus group members and the practice relevant to the epidemiology. The Korean Liver Cancer Study Group (KLCSG) and the National Cancer Center, Korea (NCC) published their own 2014 KLCSG-NCC Practice Guideline for the Management of HCC[4].

4.2 LITERATURE REVIEW

Based on a review of the current literature on clinical microwave (MW) ablation, collectively[5], the studies demonstrate that microwave ablation is a safe and effective therapy for tumors in the liver, lung, kidney and bone when compared with the current clinical standard, radiofrequency (RF) ablation. In particular, they demonstrate that microwave ablation is associated with high rates of technical success, low complication rates, low rates of local recurrence and good long-term survival. In addition, the studies illustrate several advantages of microwave ablation, including uniform cell kill within ablation zones, multiple-antenna capability, and improved perivascular ablation. The treatments were performed using multiple different microwave systems characterized by different frequencies, maximum power, antenna size, antenna design, and feed line cooling mechanism. Despite differences in system design, the studies consistently established that microwave ablation is safe and effective. While the majority of the studies focus on the use of microwaves for focal tumor ablation, several studies have demonstrated that microwaves are also an effective means of achieving precoagulation during liver resections.

Direct Comparisons Between MW and RF Liver Ablation

A number of studies have directly compared MW ablation with RF ablation for treating hepatocellular carcinoma (HCC). The results of these studies are summarized in Table 3. Earlier studies demonstrated no significant difference in rates of complications, technical success, local tumor control and survival between the two modalities. Shibata et al[6] performed the first randomized trial of percutaneous MW and RF for the treatment of patients with HCC. The study demonstrated comparable rates of technical success, complications and local progression. However, the study was limited to tumors smaller than 4 cm and had a short

follow up period.

Therefore, there was no data on survival. Lu et al[7] later published a retrospective comparison of patients with HCC treated with either percutaneous MW or RF and included tumors measuring up to 7 cm in diameter. There were no significant differences in local control or technical success between MW and RF for either tumors larger than 3 cm or for those smaller than 3 cm. The investigators followed patients for up to 51 months (mean, 25 months) and demonstrated no difference in survival up to 4 years post-ablation. One limitation of the study is the fact that each tumor initially received two treatment sessions in the MW group and only one in the RF group. Yin et al[8] treated 109 patients with larger (3-7 cm) hepatocellular carcinomas measuring up to 7 cm using either percutaneous RF or MW. This study again demonstrated that microwave ablation is as safe and effective when compared with RF ablation for the treatment of larger HCCs. Qian et al[9] prospectively compared the clinical efficacy of MW and RF for treating small (< 3cm) HCCs. MW ablation resulted in significantly larger ablation zones. There were no significant differences in rates of technical success or local tumor progression at a mean follow-up interval of 5.1 months. Vogl et al[10] retrospectively compared the rates of technical success, residual tumor and tumor recurrence for RF and MW ablation. In that study, there was no difference in therapeutic response between the two modalities. A limitation of these earlier studies is that the microwave ablation systems used were underpowered and utilized non-cooled, large-diameter antennas.

Several recent trials have demonstrated improved local control, decreased local tumor progression rates, and/or improved survival for patients undergoing MW ablation when compared with RF. Abdelaziz et al[11] showed a trend toward improved survival with MW ablation and a significantly lower local recurrence rate for MW ablation (3.9% vs 13.5% for RF ablation). Lee et al[12] compared long-term outcomes of patients with HCC undergoing MW ablation and RF ablation via a surgical approach. Disease-free survival (DFS) and overall survival (OS) at 5 years were similar between the groups. However, 5-year overall survival was significantly higher for patients with tumors >3.5 cm in diameter who underwent MW ablation (75% vs 29%, p=0.022). Finally, Potretzke et al[13] showed an equivalent safety profile, but significantly lower rate of local tumor progression (8.8% vs 17.7%) and a trend toward improved overall survival for patients with HCC treated with MW compared with RF. Of note, patients in this last study were treated with the Certus 140 microwave ablation system.

One study by Correa-Gallego et al[14] retrospectively compared local recurrence rates for patients with liver metastases from colorectal cancer treated with either MW ablation or RF ablation using a matched cohort analysis. Local recurrence rates were significantly lower for MW ablation when compared with RF (6% vs 20%, respectively). Follow-up was significantly shorter for the MW ablation group, but Kaplan-Meier estimates of local recurrence rates at 2 years also favored MW ablation.

Table 3. Results of Trials Comparing Microwave and Radiofrequency Ablation for the treatment of HCC

Study	Modality (# of patients)	Major Complications (%)	Technical Success (%)	Local Progression (%)	Overall Survival (% at 1, 2, 3, 4, & 5 years)
Lu et al[7]	MW (49)	8.2	95	12	82, 61, 51, 37, -
	RF (53)	5.7	93	21	72, 47, 38,24, -
Shibata et al[6]	MW (36)	11	89	24	-
	RF (36)	3	96	12	-
Yin et al[8]	MW	9.2*	88	17	*See Note*
	RF		69	26	
Qian et al[9]	MW (22)	0	96	18	-
	RF (20)	0	95	15	-
Vogl et al[10]	MW (28)	0	89	5	-
	RF (25)	0	84	6	-
Abdelaziz et al[11]	MW (66)	0	96	3.9	96, 62, - , -, -
	RF (45)	0	94	13.5	68, 47, - , - , -
Lee et al[12]	MW (26)	-	-	25	96, - , 73, - , 73
	RF (47)	-	-	33	89, - , 62, - , 46
Potretzke et al[13]	MW (99)	1.0	100	8.8	-
	RF (55)	3.6	100	17.7	-

Note—Survival data given in the form of median survival, which was 30 months for MW and 19 months for RF.

* Complication rates not stratified by modality

Evaluation of MW Ablation in Liver

In addition to the comparative studies discussed above, numerous studies have established that microwave ablation is a safe and effective means of treating both primary and secondary liver tumors. The trials include patients treated percutaneously, laparoscopically or at laparotomy. The results of the studies are summarized in Table 4. Multiple earlier studies demonstrated low rates of complications and high rates of technical success and local control. Martin et al[15] treated 100 patients with 270 liver tumors using intraoperative MW ablation. While many of the patients underwent concomitant hepatectomy, the ablation specific complication rate was low (2%) and the rate of local tumor progression at a median of 36 months was 2%. Kuang et al[16] treated 90 patients with liver tumors using ultrasound-guided percutaneous MW ablation. Effective local control was achieved with a local tumor progression rate of 5% at a mean follow-up of 17.4 months. In a study by Seki et al[17], percutaneous MW ablation was used to treat liver metastases less than 3 cm in size in 15 patients with colorectal cancer. Local recurrence was seen in two patients and there were no complications. Livraghi et al[18] reported the complication rates for 736 patients undergoing MW ablation for 1037 liver tumors in 14 Italian centers. There were no deaths. The major complication rate was 2.9% and the minor complication rate was 7.3%. Lorentzen et al[19] treated 39 patients with 125 liver metastases using contrast-enhanced US-guided MW ablation. The procedures were either performed percutaneously or at laparotomy, some with concomitant liver resection. Technical success was achieved in 100% of patients with a 10% rate of local tumor progression. Only one major complication occurred, a liver abscess that resolved with percutaneous drainage.

Additional studies in Table 4 provide data regarding procedure-related complications and local control as well as data regarding survival. Dong et al[20] performed a retrospective review of 234

patients with HCC treated with percutaneous MW ablation. No major complications occurred and there was a high technical success rate (93%) and a low rate of local tumor recurrence (7% with a mean follow-up of 27.9 months). The investigators found significant differences in survival between patients with poorly differentiated HCC and those with well- differentiated HCC. Differences were also seen between patients with tumors larger than 5 cm and those with tumors smaller than 5 cm. Iannitti et al[21] reported the results of a multi-institutional clinical trial of 87 patients with 224 liver tumors who underwent open, laparoscopic or percutaneous MW ablation with either single or triple antenna configurations. The rate of local tumor recurrence was low (2.7%) at a mean follow-up of 19 months. The disease-free survival rate was 47%. Liang et al[22] published the safety and efficacy of US-guided percutaneous microwave ablation in a large series of 1007 patients with 1363 primary liver tumors. Technical success was 97% and the rate of local tumor progression was 6%. Overall survival at 1, 3, and 5 years was 91%, 73% and 60%. The major complication rate was 2.2%. Seki et al[23] treated 68 patients with HCC using laparoscopic microwave ablation. The technical success rate was high (91%) and the local recurrence rate was low (12%). The 1-, 3-, 5-year survival rates were 97%, 81% and 43%, respectively. Itoh et al[24] performed intraoperative MW ablation in 60 patients with 143 unresectable HCCs. The rates of technical success and local tumor progression were 95% and 11.6%, respectively. Five-year overall survival was 43.1%.

Additional studies have continued to add to the growing body of evidence that MW ablation is safe and effective for local control of hepatic malignancies. Jiao et al[25] reported on their experience performing MW ablation in 60 patients with 96 liver tumors. They achieved 93% technical success with a 5% local tumor progression rate at a mean follow-up of 17.7 months. Groeschl et al[26] published a high rate of technical success (95%) and low rate of tumor progression (8%) in 72 patients treated with microwave ablation for liver tumors. Liu et al[27] evaluated microwave ablation for the treatment of larger (3-8cm) HCCs. The rate of technical success was 87% with 22% local tumor progression. Median survival was 56 months. Li et al[28] reported on their experience treating 18 patients with 24 liver metastases from nasopharyngeal carcinoma. Median follow-up was 22.4 months. They achieved 100% technical success and had a median overall survival of 41.4 months. One of the 18 patients required chest tube placement for a pneumothorax.

More recent studies have continued to demonstrate that microwave ablation is safe and effective for the treatment of liver tumors with low complication rates, high rates of technical success, lower rates of local tumor progression than have historically been reported for RF, and promising disease-free and overall survival rates. Zaidi et al[29] treated 53 patients with malignant liver tumors with microwave ablation using a laparoscopic or open approach. Morbidity was 11.3% and technical success was 99.3%. The local recurrence rate was low at 0.7%. Alexander et al[30] reported on a 9-year retrospective study of 64 patients who underwent MW ablation for focal hepatic malignancies. Likelihood of local recurrence at 1 year was relatively high compared with other studies and varied by histology (39.8% for HCC to 70.8% for non-CRC metastases). Tumor size did not impact rates of complete ablation or local recurrence. Sun et al[31] reported the results of treating medium sized HCCs (3-5 cm) with microwave ablation. The technical effectiveness rate was high at 93% and the major complication rate was low at 2.7%. There was one procedure related death from an abscess related septicemia. Overall survival was 89%, 74% and 60% at 1, 2, and 3 years respectively. Eng et al[32] reported the results of treating 33 patients with colorectal cancer liver metastases using intraoperative microwave ablation. The local recurrence rate was low at 7.8% and overall survival was 35.2% at 4 years. Ziemlewicz et al[33] reported the first larger series of patients with HCC treated with the Certus 140 ablation system. Seventy-five patients with 107 tumors were treated. The technical success rate was 100% and the local tumor progression rate was

low at 8.2%. Overall survival was 76% at median follow-up of 14 months. Leung et al[35] reported outcomes of treating 176 patients with liver malignancies using microwave ablation. The local recurrence rate was low at 7.9% at a median follow-up of 20.5 months. Contrary to other recent studies, tumor size and perivascular location were associated with a higher risk of local recurrence. Finally, Wang et al[36] reported a local tumor progression rate of 11.8% and 1-year, 2-year, and 3-year overall survival rates of 98.1%, 87.1% and 78.7%, respectively, for patients with colorectal cancer liver metastases treated with ultrasound-guided percutaneous microwave ablation.

Two additional studies are worth mentioning. One looked at risk factors for local tumor progression after US- guided MW ablation of liver malignancies[34]. The patient population overlaps with other studies already discussed, but it is worth mentioning due to the sample size (2529 tumors). Overall, local tumor progression (LTP) was low at 4.2% per tumor and 8.6% per patient. They found tumor size (>3cm) to be predictive of LTP. The other compared MW ablation and transarterial chemoembolization (TACE) for large HCC (5-7 cm), a cohort not routinely treated with ablation. MW ablation was associated with a higher rate of complete response (75%) with fewer sessions, lower LTP, fewer de novo lesions, less post-treatment ascites, and higher survival rates when compared with TACE.

Table 4. Results of Studies Evaluating Hepatic Microwave Ablation for Malignant Liver Tumors

Study	Patients / tumors	Major Complications (%)	Technical Success (%)	Local Progression (%)	Overall Survival (% at 1, 2, 3, 4, & 5 years)
Martin et al[15]	100/270	2	100	2	-
Kuang et al[16]	90/133	4	93	5	-
Seki et al[17]	15/15	0	87	13	-
Livraghi et al[18]	736/1037	2.9	-	-	-
Lorentzen[19]	39/125	3	100	10	-
Dong et al[20]	234/339	0	93	7	93, 82, 73, 66, 57
Iannitti et al[21]	87/224	16*	97	2.7	*See Note*
Liang et al[22]	1007/1363	2.2	97	6	91, - , 73, - , 60
Seki et al[23]	68/71	0	91	12	97, - , 81, - , 43
Itoh et al[24]	60/143	18*	95	12	94, - , 54, - , 43
Jiao et al[25]	60/96	-	93	5	-
Groeschl et al[26]	72/157	-	95	8	-
Liu et al[27]	80/80	-	87	22	81, 68, 57, - , 35
Li et al[28]	18/24	6	100		41.4 mo (median OS)
Zaidi et al[29]	53/149	11.3*	99.3	0.7	-
Alexander et al[30]	64/64	0	95.3	-	-
Sun et al[31]	182	2.7	93	25	89, 74, 60, - , -
Eng et al[32]	33/49	24	-	7.8	35.2% @ 4 yrs
Ziemlewicz et al[33]	75/107	0	100	8.2	76% @ median 14 mo
Yu et al[34]	1209/2529	-	-	4.2	-
Leung et al[35]	176/416	-	-	7.9	58.3-79.4% @ 4 yrs
Wang et al[36]	115/165	-	-	11.8	98.1, 87.1, 78.7, - , -

Note—Survival data given in the form of percent of patients surviving and disease-free with a mean follow-up of 19 months, which was 47%.

* The total number of minor and major complications, because they were not stratified by severity.

Microwave Ablation Compared with Hepatic Resection

Shibata et al[37] conducted a randomized trial of patients with multiple resectable liver metastases from colorectal cancer who underwent either intraoperative MW ablation (14 patients) or hepatectomy (16 patients). There was no significant difference in survival rates between the two groups. The 1-, 2-, and 3-year survival rates and mean survival times were 71%, 57%, 14%, and 27 months, respectively, in the microwave group, and 69%, 56%, 23%, and 25 months, respectively, in the hepatectomy group. However, operative blood loss and the need for transfusions were significantly lower in the microwave ablation group. Recently, Zhang et al[38] compared the efficacy of liver resection with percutaneous MW ablation for patients with single small (<3 cm) HCCs. Patients (n=190) had Child Pugh A cirrhosis. Major complications were significantly higher in the resection group (22.1% vs 5.9%, p=0.004). There was no significant difference in overall survival, but the disease-free survival was significantly higher in patients who underwent resection, except for patients with portal hypertension (OS and DFS were similar between groups). Shi et al[39] compared MW ablation and surgical resection for treating patients with HCC within Milan criteria. For solitary tumors ≤ 3cm, DFS and OS were similar for patients treated with MW ablation and resection. For all patients within Milan criteria, there was no difference in OS, but resection was associated with a higher rate of DFS.

Microwave Ablation Results in Uniform Necrosis

Several treat-and-resect studies have established that microwave ablation results in uniform necrosis without any evidence of viable tissue or skip lesions within the ablation zone. Simon et al[40] performed a treat-and-resect trial on 10 patients with liver tumors and pathology demonstrated uniform absence of viable tissue within the ablation zone, including surrounding larger (> 3 cm) blood vessels. The average tumor diameter was 4.4 cm and the average ablation zone diameter was 5.5 cm. Meredith et al[41] also performed a treat-and-resect trial on liver tumors and showed complete tumor kill at the ablation/tumor interface with no viable cells within the ablation zone. Importantly both of these studies demonstrated that the ablation zone shape was not distorted by blood vessels and there was no viable perivascular tissue. Clark et al[42] performed a treat-and-resect trial in 10 patients with renal cell carcinoma (RCC) undergoing a radical nephrectomy and pathology demonstrated no viable tissue within the ablation zones. Bartoletti et al[43] also reported 100% uniform necrosis in a treat-and-resect trial of 14 patients with solid renal masses. Muto et al[44] performed laparoscopic MW ablation followed by enucleation of solitary renal masses in 10 patients. There were not periprocedural complications and uniform necrosis (no skip lesions) was seen within the ablation zone.

Multiple-Antenna MW Ablation

Several reports have demonstrated that multiple-antenna microwave ablation is safe and improves treatment efficacy. Multiple antennas were used in the studies by Simon et al[40] and Meredith et al[41] described above. In addition, Yu et al[45] treated nine patients with intraoperative MW prior to resection of HCC. The ablations were performed with a single straight antenna, three straight antennas, or three looped antennas. The coagulation volumes were significantly larger for the three-antenna configurations and the study showed that multiple antennas are a promising way to safely, rapidly and effectively treat large HCCs. Uniform cell kill within the ablation zone was also seen in this study.

4.3 RISKS AND BENEFITS ANALYSIS

Expected but rarely occurring side effects related to microwave ablation include pain, fever, ascites, nausea, vomiting, general feeling of tiredness, bleeding, seeding, thrombosis, collateral organ injury, pneumothorax, pleural effusion, pneumonia and liver failure. In addition, it is expected but rare to see minimal collection of fluid or blood in the liver and heat damage to the adjacent areas from the CT scan and other imaging done after the procedure, and this can occur without any other sign and symptom. For pregnant patients, the potential risks to the patient and/ or baby have not been established.

4.3.1 Comparison with Other Microwave Ablation Systems:

Clinical Efficacy
The Certus 140 has the same intended use as other microwave ablation systems. The power levels of the Certus 140 provide clinicians with greater flexibility than many of the other systems currently available, including the ability to drive 3 probes, in-phase, at one time as well as having a higher top end power (140 W for a single probe) than most other systems. However, the total power available does not exceed other microwave systems on the market and thus does not introduce new risks. Multiple ablation probe types are available.

New Hazards or Intended Uses:
All hazards associated with the use of the Certus 140 have been identified and appropriately mitigated. Design considerations were taken to reduce the risks associated with existing microwave ablation systems, including improved system usability and cable management. The Certus 140 does use a CO_2 cooling system where all other microwave systems use sterile water, but the risks associated with this cooling system do not differ from the risks inherent in cryogenic ablation systems, also widely accepted in clinical use. Thus, the Certus 140 does not introduce new hazards or intended uses.

Clinical Benefit:
The Certus 140 2.45 GHz Ablation System is the same fundamental science and technology as other microwave ablation systems commercially available. As noted in the literature review above, microwave ablation has been generally accepted by the clinical community to be safe and effective and thus the Certus 140 can be considered safe and effective.

To date, over 25,000 patients in the US have had ablations performed using the Certus 140 system.

The Adverse Events associated with the Certus 140 System and Probes can be categorized as follows:

1. Mechanical probe breaks due to excessive force applied during probe placement, often through and around boney structures and/or cartilage.
2. Skin burns due to user placing probe improperly close to the patient's skin or delivering power for excess time and power given the probe placement.
3. Known risks associated with thermal ablation not associated with device failure or misuse.
4. Patient developed a bronchopleural fistula after a lung ablation procedure due to user error.

Regulatory Evidence of Substantial Equivalence
Additional information of the Certus 140 substantial equivalence may be found in the product's US FDA 510(k) clearance as below:

Product	FDA 510(k) Clearance
Certus 140 (including LK, LN and SR Ablation Probes	K100744
Certus 140 (including PR Ablation probes)	K113237
Certus 140 (SW Update to add Surgical SW)	K122217
Certus 140 (including CertuSurgGT Surgical Tool)	K130399
Ablation Confirmation SW Option	K160313
Certus 140 (including 15 ga probes)	K160936

4.3.2 Comparison with Radiofrequency Ablation Systems:

The subject assessments and procedure for microwave ablation (MWA) procedure being performed with the study devices are similar to the radiofrequency ablation (RFA) procedure that subjects would receive as part of their standard of care prior to the availability of MWA at the site.

To date, there is no reported difference in the reported adverse events between RFA and MWA.

In a meta-analysis by Huo et al[47], MWA and RFA had similar 1–5-year overall survival, disease-free survival, local recurrence rate, and adverse events. In terms of adverse events, MWA and RFA have similar low rates of complications, as identified in the same meta-analysis by Huo et al, and previous systematic reviews and multicenter trials[18, 48] also found similar low rates of complications (4.1% for RFA and 4.6% for MWA).

4.3.3 Potential Benefit to Subjects:

The main benefits to Subjects from participation in this study are that they will be treated with a new microwave ablation technology, and the Sponsor will supply the study devices free of charge to the site who will treat the Subjects. There is no evidence that MWA is inferior to RFA but there is a strong suggestion that MWA is better for larger lesions[12, 49]. As a result, subjects in the study may experience an improved result over standard of care treatment with RFA. The knowledge gained from this clinical trial may also help future microwave ablation patients.

5.0 SCIENTIFIC RATIONALE

5.1 STUDY RATIONALE

While there are several treatment options for hepatocellular carcinoma, there is a limitation to current options for microwave ablation in Korea. There has been no prospective clinical trial with the study device outside of United States.

The primary focus of this study is to assess the safety and effectiveness of NeuWave Medical's Certus 140™ 2.45 GHz Ablation System, Probes and Accessories in the ablation (coagulation) of the liver in percutaneous settings. Specific goals are to monitor the completion of ablation, specifically technical success immediately after ablation and technique success during the follow-up period of 36 months, local tumor progression rate and survival rate as well as adverse events in the Korean patient population.

The results from this study are expected to provide a review of the use of devices in microwave ablation of the liver. Data acquired in this study will provide safety and technical effectiveness data and user experience in a Korean patient population. This data, along with health economic information, will provide input for future innovations within the microwave ablation pipeline and potentially influence local clinical practice guidelines for the treatment of liver cancer.

5.2 STUDY DESIGN RATIONALE

The study is designed as a prospective, non-comparative, single center study with a cohort of 30 subjects. The follow-up period of up to 36 months was selected to cover the recovery period after ablation and the recommended intensive monitoring period for evaluation of progression-free survival and overall survival.

5.3 RATIONALE OF STUDY POPULATION

Subjects at an early stage of Hepatocellular Carcinoma (HCC), with tumor size of ≥ 2 cm and up to 5 cm at a single location and suitable for percutaneous microwave ablation are targeted for this study. The rationale for limiting the population to early stage of hepatocellular carcinoma and a single tumor within this larger size range is to address the gap in the evidence for effective treatment for this category of patients. For patients at an early stage of hepatocellular carcinoma and with tumor size ≤ 3 cm, curative treatment options could be resection, liver transplantation or ablation as per treatment guidelines. However, there is no clear evidence for effective treatment of larger than 3 cm lesions, and the efficacy of RFA in this category is not established. Hence, only 7 patients with HCC and tumor size > 3 cm were treated with RFA at the qualified study center in 2016. To ensure sufficient enrollment for this study, subjects with tumor size of ≥ 2 cm and up to 5 cm will also be included.

This study will provide clinical evidence of the use of microwave ablation in unresectable cases which still have relatively good liver function (Child Pugh Score of Class A or B) and slightly larger tumor size of ≥ 2 cm and up to 5 cm. The physician should consider using multiple probes for lesions ≥ 2 cm.

6.0 STUDY OBJECTIVE

To evaluate the outcomes of microwave ablation of Hepatocellular Carcinoma (HCC) of more than 2 cm and up to 5 cm.

6.1 PRIMARY OBJECTIVE

- Evaluate the technical success of microwave ablation of Hepatocellular Carcinoma (HCC) of ≥ 2 cm and up to 5 cm, using NeuWave Medical's Certus 140™ 2.45 GHz Ablation System and Accessories (study devices), immediately following the ablation procedure.

6.2 SECONDARY OBJECTIVES

- Evaluate the primary technique efficacy at 1 month after the ablation procedure.
- Evaluate local tumor progression (LTP)[50] rate at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months after the ablation of the index tumor.
- Evaluate the primary efficacy rate[50].
- Evaluate the secondary efficacy rate[50].
- Evaluate the progression free survival and overall survival rates at 36 months after the ablation procedure.
- Evaluate safety through the type and frequency of adverse events through 3 months and cumulatively through study completion.
- Evaluate quality of life before the ablation procedure and at each post-ablation visit.
- Evaluate the health economics associated with the ablation procedure

7.0 STUDY DESIGN

7.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

This prospective, single-arm single center study will provide clinical data using the study devices. Individuals scheduled for microwave ablation of the liver in accordance with their institution's SOC, and who meet study entry criteria, will be screened for enrollment after providing informed consent. Subjects will be followed for up to 36 months following the ablation procedure for safety and outcomes. Prospective subjects will be informed about the nature of the research, given the Informed Consent Form (ICF) to read, and if the subject understands the consent, will be asked to provide written consent (the ICF).

Enrollment will continue until 30 eligible subjects complete the 3-month visit after ablation (Visit 4) for the primary effectiveness and safety analysis.

Additionally, in order to reduce the variability between investigators in assessing the CT images (and, as needed, MRI and Ultrasound) and to minimize potential bias, an independent radiologist reviewer from the participating site, and who is not an investigator, will conduct a review of all the CT scans taken from screening and throughout the clinical study. The assessment by the independent reviewer will only be used for the purpose of statistical analysis while the assessment by the investigators will be used for the treatment of the subjects in the study.

7.2 STUDY ENDPOINTS

Primary:

Technical Success, defined as complete tumor ablation with adequate or insufficient margin, based on contrast-enhanced MRI and CT scans immediately following the ablation procedure.

Secondary:

- Primary Technique Efficacy, defined as complete tumor ablation with adequate or insufficient ablation margin, based on contrast-enhanced MRI and CT scans follow-up at 1 month after the ablation procedure;
- Local tumor progression (LTP) rate, evaluated at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months after the ablation of the index tumor;
- Primary efficacy rate, defined as the percentage of target tumors successfully eradicated following the ablation procedure;
- Secondary efficacy rate, defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression;
- Progression free survival and overall survival rates at 36 months after the ablation procedure;
- Rate of adverse events reported through 3 months and cumulatively through study completion; Quality of Life, as measured by VAS pain score, EORTC QLQ-C30 and EORTC QLQ-HCC18, before the ablation procedure and at each post-ablation visit;
- Health economics associated with the ablation procedure: complete procedure time, ablation time, no. of ablations, length of stay, no. and types of probes used.

7.3 SITE QUALIFICATION

The qualified study center will have experienced researchers familiar with laws, regulations and good clinical practice guidelines applicable to Korea, and interventional radiologist(s)

experienced with the use of microwave and/ or radiofrequency ablation devices in the liver.

Each site must provide all documentation required by the Sponsor's Site Initiation procedure (refer to section 12.2) prior to consenting and enrolling the first subject.

7.4 TRAINING FOR PROSPECTIVE STUDY TREATMENT

All Investigators and staff involved in the ablation procedure must undergo standard device inservicing/ training prior to treatment of first subject. Additional training may be performed at the request of the Sponsor or study staff. Investigators using the study device will be trained on the Instructions For Use (IFU).

All Investigators and those to whom the Investigator delegates study responsibilities will be trained on the protocol by a representative of the Sponsor.

8.0 STUDY POPULATION

Subjects will be selected for recruitment into this study from patients who are scheduled for microwave ablation of the liver in accordance with their institution's SOC, and who meet general study entry criteria. A subject will be considered enrolled after signing the study's informed consent forms (ICFs).

Enrollment will continue until 30 eligible subjects have been treated with Neuwave microwave ablation and have completed the 3-month visit (Visit 4). One center in Korea will be selected as study site. No study-related procedure or form associated with this study can be completed until informed consent is obtained for that Subject.

8.1 INCLUSION CRITERIA

1. Confirmed hepatocellular carcinoma, tumor size of ≥ 2cm and up to 5 cm, single location, BCLC Stage A based on imaging (CT Scan/ MRI/ ultrasound) and biopsy confirmation in accordance with their institution's SOC procedure;
2. Primary hepatocellular carcinoma or recurrent hepatocellular carcinoma which was previously treated with ablation or surgical resection only;
3. Scheduled for microwave ablation of the liver;
4. Performance status 0-2 (Eastern Cooperative Oncology Group classification);
5. Functional hepatic reserve based on the Child-Pugh score (Class A or B)
6. ASA score ≤ 3;
7. Has given voluntary, written informed consent to participate in this study and has authorized the transfer of his/her information to the Sponsor, and willing to comply with study-related evaluation and treatment schedule; and
8. At least 19 years of age.

8.2 EXCLUSION CRITERIA

Subjects will be excluded from the study for any of the following:

1. Active (subject currently receiving systemic treatment) bacterial infection or fungal infection;
2. Systemic administration (intravenous or oral) of steroids, including herbal supplements that contain steroids, within 30 days prior to the study procedure;
3. Chemotherapy or radiation therapy for hepatocellular carcinoma may not be performed for 30 days prior to the study procedure;
4. Subject with implantable pacemakers or other electronic implants;
5. Planned/ scheduled liver surgery;
6. Subject with a platelet count of less than 50,000/$mm^{3;}$
7. Subject with an INR greater than 1.5;
8. Subject with renal failure on renal dialysis;
9. Scheduled concurrent procedure other than microwave ablation in the liver;
10. The subject is a female who is pregnant or breastfeeding;
11. Physical or psychological condition which would impair study participation;
12. Participation in any other clinical study concurrently or within the last 3 months;
13. The subject is judged unsuitable for study participation by the Investigator for any other reason; or
14. Unable or unwilling to attend follow-up visits and examinations.

8.3 PRIOR AND CONCOMITANT THERAPY

Excluding chemotherapy or radiation therapy (up to 30 days prior to procedure), study subjects may continue with their current medical care while in the study, including medications. All concomitant medications will be collected for this study.

8.4 SCREENING FAILURES

All subjects who have signed study consent but do not meet the inclusion/exclusion criteria and, therefore, have not initiated the study ablation procedure will be recorded as screen failures. The relevant electronic Case Report Form (eCRF) pages (demographics, reason for screen failure) will be completed for all screen failure subjects and, therefore, the data will be included in the study database.

8.5 REMOVAL OF SUBJECTS FROM STUDY

In accordance with the Declaration of Helsinki and Guideline for ICH and Korean GCP, 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, all efforts will be made to collect any adverse events they have experienced, if applicable.

Subject participation may be terminated prior to completing the study (i.e., the 3-year follow-up visit) for any of the reasons listed below (reasons that do not fit the categories below will be documented as "other"). Any adverse events which are ongoing at the time of discontinuation must be followed until resolution or until they become stable but ongoing. The relevant electronic Case Report Form (eCRF) pages (Study Exit, Adverse Event) will be completed for all withdrawn subjects and the data will therefore be included in the study database.

Subject Choice:
If a subject chooses to withdraw early from the study, the eCRF study completion 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.

Intra-treatment:
The Investigator must withdraw a subject during the procedure for one of the following reasons:

- Intra-treatment event that results in conversion to a surgical procedure or other procedure prior to the start of microwave ablation.

Post-treatment:
The Investigator must withdraw a subject after the procedure for one of the following reasons:

- **Concomitant medication/ procedure:**
  - Chemotherapy or radiation therapy for hepatocellular carcinoma may not be performed for 30 days after the procedure

- **Death:**
  - When possible, the cause of death will be documented.

- **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.
Subjects who withdraw or are terminated early from the study will be replaced until 30 eligible subjects complete the 3-month visit after ablation (Visit 4).

8.6 SITE TERMINATION OR STUDY TERMINATION

A site or study may be terminated. 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 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 subjects at a site or for the study as a whole; and
- Regulatory Body Mandate(s).
- The Investigator has the right to terminate their participation at any time. Should this be necessary, procedures for termination will be provided by the Sponsor.

8.7 SUBJECT COMPLIANCE

Study site personnel will make preemptive contact with subjects as necessary to ensure compliance with the follow-up schedule.

9.0 STUDY PROCEDURES

9.1 PROCEDURE DESCRIPTION

A multi-disciplinary team at the site will determine with the help of imaging, whether a patient is suitable for local ablation therapy, and the type of ablation procedure that is required, based on the stage, location and cell types associated with the liver tumor. Potential candidates for microwave ablation will undergo liver, renal function, coagulation, Alpha-fetoprotein (AFP) and CBC tests before the procedure to ensure that they will have adequate liver capacity following the ablation.

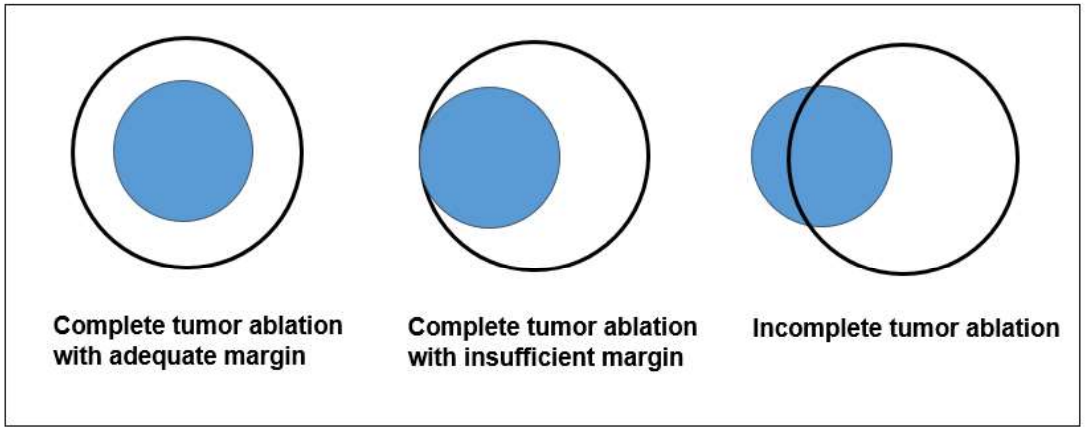
Microwave Ablation Procedure

All ablations will be performed under general anesthesia with deep sedation via percutaneous approach by trained interventional radiologists who are experienced with tumor ablation. Microwave ablation is a minimally invasive procedure that uses electromagnetic waves to generate tissue necrosis in the liver in this study. Using contrast-enhanced ultrasound imaging guidance, a small probe is inserted percutaneously into the lesion.

The ablation will be performed with a single high-powered, gas-cooled, multiple antenna–capable microwave system (NeuWave Medical's Certus 140™ 2.45 GHz Ablation System) with single or multi-probe antennas, according to the IFU and the performing physician's clinical judgment. Electromagnetic waves are delivered to the tissue, producing frictional heating to generate tissue necrosis at > 60°C. Duration of treatment and power application will be determined by the performing physician based on manufacturer guidelines, with adjustment for tumor size, proximity to vulnerable structures, and real-time intraprocedural monitoring. Antenna placement will be performed under real-time contrast- enhanced ultrasound imaging guidance. Single or multiple ablation sessions may be done in one procedure. It is suggested that the physician considers using more than one probe for lesions ≥ 2 cm.

At the end of the ablation, contrast-enhanced MRI and CT scans will be done to confirm the completion of the ablation procedure (up to 4 days after the date of the ablation procedure). According to the standard practice at the site in Korea, ablation confirmation will be classified as:

- complete tumor ablation with adequate margin
- complete tumor ablation with insufficient margin
- incomplete tumor ablation.



10.0 STUDY DEVICES

For this study, medical devices will be provided to the site by the Sponsor and will be used according to the site's standard of care (SOC) and in accordance with manufacturer design specifications, product instructions and guidelines. Any one of the following devices will be applicable for documentation in this study:

10.1 PRODUCT OVERVIEW

10.1.1 System Overview

The system has a single 2.45 GHz signal microwave source generator and three (3) independent microwave amplifiers, each capable of producing up to 140W each. Generator power is limited based upon the number of probes selected and the types of probes used. One touch-screen user interface controls the system. The User Interface can be set for either Ablation Mode or Surgical Mode. Up to three (3) microwave ablation probes can be connected to and powered by the system at one time. An intermediate junction box or Power Distribution Module (PDM) reduces system set up complexity.

10.1.2 Cooling System Overview

A CO_2 based cooling system ensures the non-active portion of the probe does not exceed temperature requirements. Additionally, the CO_2 enables the Tissu-Loc function, which can be used to adhere or stick the probe in place prior to starting ablation therapy. This function is similar in use to the stick function available on cryogenic ablation systems.

The system uses two (2) E-sized CO_2 cylinders. When a tank in use empties, the system will automatically switch to using the other tank and notify the user to replace the empty tank.

The cooling system regulates the flow of high pressure CO_2 in a cooling gas tube to the PDM and eventually to the probe. Inside the tip of the probe, the cooling gas tube expands from high pressure to low pressure. As the gas pressure reduces quickly, the Joule-Thompson effect causes the probe shaft to cool. This is used for both the Tissu-Loc™ function and to keep probes at a safe temperature while energy is being delivered to the patient.

The PDM is designed to improve the usability of the system by reducing set-up complexity while also helping to minimize the cabling from the probe to the generator. The PDM also allows a larger, lower-loss cable to be used between the microwave generator and PDM. The increased efficiency of the larger cable and PDM allow more power to be safely sent to the ablation probe without an unsafe heating of the probe cable or handle.

System performance is constantly monitored. The Certus 140 Ablation System will automatically discontinue delivering microwave energy in the event of system failures.

10.1.3 Probes Overview

Probes are provided sterile and are intended for single patient use only. Ablation probes are comprised of a sharp trocar on the end of a cannula, a probe handle, a 1.4-meter cable, and a connector assembly.

Each probe contains three (3) temperature measurement sensors that help monitor performance and ensure patient and operator safety. Additionally, the different percutaneous ablation probes have been designed to optimize the energy transfer efficiency from the probe into different types of tissue based on known electrical properties of each tissue.

The ablation probe assembly contains 4 main sections: a handle, a cannula, a radiating section and a faceted tip for insertion. The probes have a triaxial antenna design. The triaxial antenna design is created from a coaxial monopole antenna passed through a hollow needle. The needle creates the triaxial structure and its tip is positioned approximately ¼ of a wavelength proximal to the monopole base. This positioning improves antenna efficiency and reduces fields flowing back on the coaxial outer conductor. In turn, more energy is deposited in the tissue. Additionally, different ablation probes have been designed to optimize the energy transfer efficiency from the probe into different types of tissue based on known electrical properties of each tissue.

Models CertusLK and CertusPR have either a 17-gauge or 15-gauge cannula and are available in 15 cm and 20 cm lengths. These probes have a cable length of 1.4 m.

CertusLK probes are designed to perform optimally, in terms of efficiently transferring energy into tissue, in liver and kidney tissue.

The antenna of the CertusPR probe is designed to limit the length of the ablation for instances when a shorter ablation zone is desired. CertusPR Probes were developed to provide physicians with an additional ablation probe designed specifically for ablating smaller lesions. The CertusPR probes are designed to produce ablations that quickly encompass the tip of the probe while limiting the overall length of the ablation. CertusPR probes will enable physicians to ablate smaller lesions while limiting necrosis of adjacent tissue when compared to other Certus probes.

An accessory, a small plastic probe clip that can hold two 17-gauge probes and allow the user to easily hold both while performing planar coagulation, is available.

10.2 PACKAGING AND LABELING

During this study, the study devices will be cleared for marketing by the Ministry of Food and Drug Safety (MFDS) in Korea, and are labeled in accordance with the Medical Device Act[51, 52]. They will be used in accordance with product labeling and IFU.

10.3 PRODUCT ACCOUNTABILITY

All devices 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 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. Details of the product code and lot numbers must be documented in the CRF as well as the subject's hospital notes. The Principal Investigator must allow the Monitor access to the secure facility where the study devices are stored during the clinical trial in order to check inventory. At the end of the clinical trial all unused study devices must be returned to Johnson & Johnson Medical Korea with the appropriate study device return form. If this is as a result of a Product Complaint for the study devices, the Product Complaint form must be completed.

11.0 STUDY SCHEDULE

11.1 VISIT 1 – SCREENING

The screening activities for this visit may occur over several dates within 5 weeks prior to day of ablation.

Subjects will be evaluated according to the Investigator's standard of care practice. Subjects will be selected for microwave ablation based on the pre-procedure investigations and the Investigator's interpretation of the clinical picture. Eligible subjects will be provided with the study information including the ICF.

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

- The subject must be given ample time to review and sign the ICF;
- Collection of demographic information (age at time of consent, gender, race, ethnicity);
- Review and collection of medical and surgical history including current medical conditions (note: HCC diagnosis does not need to be reported as medical history);
- CT Scan of the liver (within 37 days prior to the screening visit)- the subject does not need to repeat a CT scan of the liver at the screening visit if the CT scan based on SOC was done within 30 days prior to the screening visit date;
- Ultrasound of the liver for planning of the ablation procedure (on the day of the visit or up to 7 days prior to the screening visit);
- Laboratory tests (within 37 days prior to the screening visit)- the subject does not need to repeat the following laboratory tests at the screening visit if these tests based on SOC were done within 37 days prior to the screening visit date:
    - Alpha-fetoprotein (AFP) test;
    - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
    - Coagulation test (PT, APTT, and INR);
    - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
    - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
    - Complete Blood Count (CBC) (differential cell count and platelet count);
    - Pregnancy test- for women of child bearing potential only.
- Tumor details (size, type, location) and BCLC Staging (pre-procedure staging);
- Evaluation of ECOG Performance Status and Child-Pugh score;
- Collection of concomitant medications (including any medication taken within 30 days prior to the screening visit);
- Review/collection of inclusion/exclusion criteria and determination as to whether the subject is eligible for participation (retrospective data, per site SOC, is permitted to determine eligibility).

11.2 VISIT 2A – PRE-ABLATION

The following data must be collected prior to the study procedure:

- Quality of Life questionnaires: VAS pain score，EORTC QLQ-C30 and EORTC QLQ-HCC18;
- Any update to medical/ surgical history;
- Any update to concomitant medications;

- Laboratory tests:
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);
- Evaluation of ECOG Performance Status and ASA score;
- Confirm inclusion and exclusion criteria;
- Date and time of hospital admission.

11.3 VISIT 2B- ABLATION

Data collected during procedure:

- Tumor details (size, type, location) and BCLC Staging (intra-procedure staging);
- Procedure details (ultrasound-guided):
  - Duration of procedure (first probe placement to last probe removal);
  - Duration of ablation;
  - Procedure performed;
  - Anatomical location of ablation;
  - Number of ultrasound scans performed for needle and margin assessment;
  - Number of needle placement attempts per needle;
  - Number of ablations;
  - Ablation settings (power and time);

  Some of the above ablation procedure details will be provided to the site via a report generated from NeuWave Medical's Call Home Database. The study site will review the report and enter the procedure details into the clinical database, as applicable.
- Device accountability: Type(s) and no. of probes used;
- MRI and CT scans of the liver (up to 4 days after completion of procedure to confirm complete tumor ablation);
- All Adverse Events and SAEs (if applicable);
- Any update to concomitant medications.

11.4 VISIT 2C- POST-ABLATION

Data collected after the procedure up to discharge from the hospital:

- Quality of Life questionnaire: VAS pain score (at discharge)
- Laboratory tests:
  - Alpha-fetoprotein (AFP) test;
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);
- Date and time of hospital discharge
- All Adverse Events and SAEs (if applicable)

- Any update to concomitant medications and procedures

11.5 VISIT 3 (1 MONTH AFTER ABLATION)

The following data will be collected during this follow-up visit:

- Quality of Life questionnaires: VAS pain score，EORTC QLQ-C30 and EORTC QLQ-HCC18;
- Evaluation of ECOG Performance Status;
- MRI and CT scans of the liver (within 14 days prior to the visit):
  - Complete tumor ablation evaluation, including LTP;
  - Indication for repeat ablation (if applicable);
- Laboratory tests (within 14 days prior to the visit):
  - Alpha-fetoprotein (AFP) test;
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);
- Follow-up post-ablation treatment (if applicable);
- All Adverse Events and SAEs (if applicable);
- Any update to concomitant medications and procedures.

11.6 VISIT 4 (3 MONTHS AFTER ABLATION)

The following data will be collected during this follow-up visit:

- Quality of Life questionnaires: VAS pain score，EORTC QLQ-C30 and EORTC QLQ-HCC18;
- Evaluation of ECOG Performance Status;
- CT scan of the liver (within 14 days prior to the visit):
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Laboratory tests (within 14 days prior to the visit):
  - Alpha-fetoprotein (AFP) test;
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);
- MRI of the liver (once per year of follow-up if applicable, depending on each subject's condition and based on the clinical judgement of the Investigator)
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Follow-up post-ablation treatment (if applicable);
- All Adverse Events and SAEs (if applicable);
- Any update to concomitant medications and procedures.

11.7 VISITS 5 TO 10- FOLLOW-UP (6 MONTHS, 9 MONTHS, 1 YEAR, 18 MONTHS, 2 YEARS, AND 30 MONTHS AFTER ABLATION)

The following data will be collected during each follow-up visit:

- Quality of Life questionnaires: VAS pain score，EORTC QLQ-C30 and EORTC QLQ-HCC18;
- Evaluation of ECOG Performance Status;
- CT Scan of the liver (within 14 days prior to the visit)
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Laboratory tests (within 14 days prior to the visit):
  - Alpha-fetoprotein (AFP) test;
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);
- MRI of the liver (once per year of follow-up if applicable, depending on each subject's condition and based on the clinical judgement of the Investigator):
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Follow-up post-ablation treatment (if applicable);
- Subjects will be evaluated for all adverse events according to the Investigator's standard of care practice during each follow-up visit. Note that for this study, after Visit 4 (3 months), only expected or unexpected serious adverse device effects, life-threatening events, events that result in death and all SAEs with definite, possible, probable or unknown relationship to the study device or study procedure will be reported to the Sponsor, if applicable;
- Any update to concomitant medications and procedures.

11.8 VISIT 11- END OF STUDY VISIT (3 YEARS AFTER ABLATION)

The following data will be collected during the final follow-up visit:

- Quality of Life questionnaires: VAS pain score，EORTC QLQ-C30 and EORTC QLQ-HCC18;
- Evaluation of ECOG Performance Status;
- CT Scan of the liver (within 14 days prior to the visit)
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Laboratory tests (within 14 days prior to the visit):
  - Alpha-fetoprotein (AFP) test;
  - Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II);
  - Coagulation test (PT, APTT, and INR);
  - Liver function test (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, total protein);
  - Renal function test (BUN, Creatinine and electrolytes (sodium, potassium, and chloride));
  - Complete Blood Count (CBC) (differential cell count and platelet count);

- MRI of the liver (once per year of follow-up if applicable, depending on each subject's condition and based on the clinical judgement of the Investigator)
  - LTP evaluation;
  - Indication for repeat ablation (if applicable);
- Follow-up post-ablation treatment (if applicable);
- Subjects will be evaluated for all adverse events according to the Investigator's standard of care practice during each follow-up visit. Note that for this study, after Visit 4 (3 months), only expected or unexpected serious adverse device effects, life-threatening events, events that result in death and all SAEs with definite, possible, probable or unknown relationship to the study device or study procedure will be reported to the Sponsor, if applicable;
- Any update to concomitant medications and procedures;
- Date of study completion.

11.9 UNSCHEDULED VISIT

Unscheduled visits are for those that are procedure, device, or disease related.
The following data will be collected during each unscheduled visit:

- Reason for the unscheduled visit;
- Follow-up post-ablation treatment (if applicable);
- Adverse Events (if applicable). Subjects will be evaluated for all adverse events according to the Investigator's standard of care practice during each follow-up visit. Note that for this study, from study treatment to Visit 4 (3 months), all AEs and SAEs will be reported to the Sponsor, and after Visit 4 (3 months), only expected or unexpected serious adverse device effects, life-threatening events, events that result in death and all SAEs with definite, possible, probable or unknown relationship to the study device or study procedure will be reported to the Sponsor, if applicable;
- Any update to concomitant medications and procedures.

11.10 REDUCED FOLLOW-UP VISIT

This visit can be a clinic visit or a phone contact visit which will occur every 6 months (+/-28 days) from the day of the first ablation. The following data will be collected only for subjects who have progressed or recurred following the first ablation and are retreated with any treatment post progression:

- Follow-up post-ablation treatment (if applicable);
- Any additional progression(s)/ recurrence(s);
- Survival status;
- Adverse Events (if applicable). Subjects will be evaluated for all adverse events according to the Investigator's standard of care practice during each follow-up visit. Note that for this study, after Visit 4 (3 months), only expected or unexpected serious adverse device effects, life-threatening events, events that result in death and all SAEs with definite, possible, probable or unknown relationship to the study device or study procedure will be reported to the Sponsor, if applicable;
- QOL questionnaires

For subjects on the Reduced Follow-up schedule 6 monthly visits occur until approximately 3 years post ablation.

11.11 INDEPENDENT REVIEWER (IR)

An Independent Reviewer, from the site in Korea, will be utilized in this clinical trial in order to

reduce the variability between investigators in assessing the CT images (and as needed, MRI and Ultrasound) and to minimize potential bias. The Independent Reviewer will review all CT scans taken throughout the study (including at screening) using the images stored in the hospital's database and without referring to the radiology imaging report in order to avoid influence in the assessment. All images will be taken in accordance with the hospital's Standard of Care. At baseline, the independent reviewer will confirm the presence of one lesion, and its location, size, and BCLC stage.

According to the standard practice at the site in Korea, the independent review will classify the ablation as:

- complete tumor ablation with adequate margin
- complete tumor ablation with insufficient margin
- incomplete tumor ablation.

This assessment will be done for the scans taken following the ablation procedure (Visit 2, for technical success) and at the 1-month visit (Visit 3, for technical efficacy).

At all post-ablation follow up visits, the central reviewer will assess recurrence of the target lesion, progression, meaning a new lesion(s), or lack thereof. If there is a progression or recurrence, the central reviewer will again assess number of lesions, location, size and BCLC stage.

The assessment by the independent reviewer will only be used for the purpose of statistical analysis while the assessment by the investigators will be used for the treatment of the subjects in the study as well as reported in the analysis.

12.0 ASSESSMENT OF SAFETY

12.1 ADVERSE EVENT REPORTING

Adverse Events associated with the device, or the procedure, and incidents such as those specified in local laws and regulations, including Korean Guidelines for GCP[53], will be captured and reported during this study. Monitoring of study sites by Sponsor personnel will ensure that adverse events, and product complaints are documented.

12.1.1 Definitions

12.1.1.1 Pre-existing Condition

A pre-existing condition is one that is present at the start of the study, and is to be reported as part of the subject's medical history. It must be reported as a new Adverse Event if the intensity, frequency, or the character of the condition worsens during the study treatment.

To avoid confusing pre-existing conditions with AEs during data analysis, the study sites must make all attempts to provide start dates for all baseline medical conditions. Any pre-existing condition that has worsened in intensity, frequency, or the character of the condition should be recorded on the AE eCRF as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

12.1.1.2 Adverse Event

An AE is an untoward medical occurrence (sign, symptom or disease) in a patient or clinical trial subject and which does not necessarily have a causal relationship with the study medical device. An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition, which occurs at any point from study treatment to Visit 11.

Note: A local tumor progression by itself should be considered a progression of disease (pre-existing condition). Progression of disease does not meet the definition of an AE.

All reportable AEs must be reported to the Sponsor within 2 weeks of the site becoming aware.

12.1.1.3 Adverse Device Effect (ADE)

An Adverse Device Effect is an adverse event related to the use of a study medical device. This includes any adverse event resulting from insufficient or inadequate Instructions for Use, deployment, implantation, or operation, or any malfunction of the study medical device and also includes any event resulting from use error or from intentional misuse of the study medical device.

ADEs must be reported to the Sponsor within 2 weeks of the site becoming aware.

12.1.1.4 Unexpected Adverse Device Effect

An unexpected ADE is an adverse device effect, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure or product labeling).

All unexpected ADEs must be reported to the Sponsor within 72 hours of the site becoming aware.

12.1.1.5 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that:

1) Results in death or is life-threatening,
2) Requires inpatient hospitalization or prolongation of hospitalization,
3) Results in persistent or significant disability/ incapacity, or
4) Results in a congenital anomaly/ birth defect.

Note:

- "Death" should not be reported as an AE. The cause of death should be reported as the AE. The only exception is "Sudden Death" when the cause is unknown.
- Planned hospitalization or procedure for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

All reportable SAEs must be reported to the Sponsor within 24 hours of the site becoming aware.

12.1.1.6 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

All SADEs must be reported to the Sponsor within 24 hours of the site becoming aware.

12.1.1.7 Unexpected Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Expected serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the IFU and IB.

All USADEs must be reported to the Sponsor within 24 hours of the site becoming aware.

12.1.1.8 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 following guideline should be used to determine the severity of each adverse event:

- **MILD:** Awareness of experience, but easily tolerated. No medical intervention required.
- **MODERATE:** Enough discomfort to interfere with usual activities. Medical intervention required.
- **SEVERE**: Inability to carry out usual activities. Medical intervention (including

hospitalization or prolongation of hospitalization) required.

12.1.1.9 Relationship/Attribution of Adverse Events

It is the Investigator's responsibility to assess the relationship of an AE to the study procedure (microwave ablation) and study device(s).

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

- **NOT RELATED:** The event is due to extraneous causes.
- **POSSIBLY RELATED:** The event is unlikely associated, but cannot be ruled out with certainty.
- **PROBABLY RELATED:** The event is likely associated, but another cause cannot be ruled out with certainty.
- **DEFINITELY RELATED:** The event is associated with a high degree of certainty; or
- **UNKNOWN:** The event cannot be defined by the categories listed above.

12.1.1.10 Complications

A major complication is defined as an event that leads to substantial morbidity and disability (e.g., results in the unexpected loss of an organ) that increases the level of care, or results in hospital admission, or substantially lengthens the hospital stay (SIR classifications C–E). This includes any case in which a blood transfusion or interventional drainage procedure is required. All other complications are considered minor. It is important to stress that several complications such as pneumothorax or tumor seeding can be either a major or minor complication depending on severity. For tumor seeding this would depend on whether or not the ectopic tumor focus can be successfully ablated or otherwise treated.

Table 5: SIR Classification System for Complications by Outcome[54]

Minor Complications A. No therapy, no consequence B. Nominal therapy, no consequence; includes overnight admission for observation only.
Major Complications C. Require therapy, minor hospitalization (< 48 hours) D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours) E. Permanent adverse sequelae F. Death.

Complications are differentiated as:

- Immediate complications: Up to 6–24 hours following the procedure
- Periprocedural complications: Within 30 days, and
- Delayed complications: Greater than 30 days after ablation.

Ablation-related complications should include problems encountered within the periprocedural (30–day) time period that can be related in any way to the procedure, as well as additional complications that were identified at delayed follow-up imaging

that were judged to be highly likely due to the ablation therapy (biliary ductal stricture, tumor seeding along the needle track, etc.).

12.1.1.11 Reporting Adverse Events

Investigator's Responsibility:
The Investigator is required to report all AEs experienced by the subject from Visit 2B until the subject completes Visit 4 (3 months after the ablation procedure) or withdraws before Visit 4. All AEs during this time period, regardless of their relatedness to the study device(s) or procedure, must be reported in the AE eCRF within 2 weeks after the site becomes aware of the information. 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 subject's medical record/source document. All AEs must be followed until resolution or until they become stable but ongoing.

Sponsor's Responsibility:
The Sponsor will follow MFDS's guideline to report safety events related to the study medical devices with the timeline which is regulated by law.

12.1.1.12 Reporting Serious Adverse Events

Investigator's Responsibility:
The Investigator is required to complete the AE eCRF for:

- All SAEs experienced by the subject from Visit 2B until the subject completes Visit 4 (3 months after the ablation procedure) or withdraws before Visit 4
- All expected and unexpected serious adverse device effects experienced by the subject, all life-threatening events, event that results in death and all SAEs with definite, probable, possible, or unknown relationship to the study device or study procedure after Visit 4 until the subject completes Visit 11 or withdraws before Visit 11.

All serious adverse events must be reported to the Sponsor by the site within 24 hours after the site becomes aware of the information by entering the data into the AE eCRF. The Investigator must avoid disclosing the subject information, by using the ID code, instead of using name, or home address. In case of death, the Investigator has to report as much information as there is available to the Sponsor, including the death certificate and/ or autopsy report (only when autopsy is performed).

The Investigator must report all expected and unexpected serious adverse device effects, and all life threatening events and events resulting in death to the IRB within the timelines regulated by their IRB procedures.

Sponsor's Responsibility:
The Sponsor will follow MFDS's guideline to report safety events related to the study medical devices with the timeline which is regulated by law.

12.2 PRODUCT COMPLAINTS

12.2.1 Product Complaints 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:

- Product contamination;
- Defective components;
- Poor packaging or product mix-up;
- Questionable stability;
- Device malfunction (the failure of a device to perform as intended for this study);
- Labeling concerns
- User errors

12.2.2 Reporting Product Complaints for Ethicon Study Devices

Product complaints related to or possibly related to the study devices must be reported to the Sponsor by completing the Product Complaint form in a timely manner, preferably within 24 hours after becoming aware of the event. If an Ethicon and /or JJMK representative is made aware of a product complaint related to the study device, the event should be reported within 24 hours of their awareness. The device concerned should be retained. Ethicon and /or JJMK representatives will organize collection of the device for evaluation.

Product Complaint forms related to the study device should be emailed to:

[redacted]

12.2.3 Reporting Product Complaints for Non-Ethicon Devices

In compliance with the requirements of local regulations describing the handling of product complaints, if a device other than the study devices (Neuwave Certus 140™ 2.45 GHz Ablation System and Accessories) malfunctioned, follow the manufacturer's instructions and do not report as a product complaint on the eCRF or to Ethicon or to JJMK, and report to the corresponding company/manufacturer.

13.0 INVESTIGATOR RESPONSIBILITIES

13.1 GOOD CLINICAL PRACTICES

An Investigator is responsible for ensuring that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH GCP, the signed Clinical Study Agreement, this Protocol, the institution's Institutional Review Board (IRB) policies and procedures, and applicable regulatory requirements.

Prior to the initiation of this clinical investigation at each site, the responsible Principal Investigator will approve this Protocol by signing the signature page. This signature confirms that the clinical trial will be performed in compliance with the Protocol.

13.2 INSTITUTIONAL REVIEW BOARD

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

Required Documentation

Documents that must be provided to the Sponsor prior to study start are as follows:

1. A copy of the formal written notification to the Investigator regarding approval of the protocol by an IRB that is in compliance with regulatory guidelines;
2. A copy of the IRB approved informed consent form and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of IRB approval of these items;
3. Name and address of the IRB, and a current list of the IRB members. If accompanied by a letter of explanation from the IRB, a general statement may be substituted for this list, or a general assurance number.
4. Applicable local regulatory documentation;
5. Signed and dated protocol Investigator Signature page;
6. Signed confidentiality agreement between the Investigator and the Sponsor;
7. Signed and dated clinical study agreement, including financial agreement; and
8. Up-to-date signed and dated curriculum vitae for each investigator and sub-investigator.

Other documents may also be required prior to the study, and during the course of the study.

13.3 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. For this study, a subject must be consented before completing any study-specific procedures. Screening information that are part of Standard of Care (SOC) procedures may occur/ collected prior to consent as they are, but the data may not be collected for study purposes until the ICF has been signed by the subject. A subject will be considered enrolled upon signing the study's informed consent form

(ICF).

An IRB-approved informed consent must be sought from each subject and must be appropriately documented in the subject's medical record. It is the Investigator's responsibility to obtain written informed consent from the subject prior to study-specific procedures. 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 approval before implementation. Each subject will be required to sign any amended ICF (as required by the IRB) and will receive a copy of the signed ICF. A set of original signed ICFs will be kept at the site.

13.4 DATA HANDLING AND RECORD KEEPING

13.4.1 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, 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.

Another type of source documents is data from NeuWave Medical's Call Home Database. NEUWAVE 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, after the conclusion of each ablation procedure; this information is collectively called the "Call Home Database." The procedure data includes, but not limited to, the following: date and time of procedure, anatomical location of ablations, number of ablations and power used for each ablation, type of probes used, the amount of contrast used (if applicable), and duration of procedure (first probe placement to last probe removal). Some of these relevant ablation procedure details will be provided to the site via a report generated from Call Home Database. 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.

Only for those subjects that specifically consent, some of the treatment and outcome data that is already being captured for this study will also be compiled with the same type of

data from consenting subjects from other NeuWave Medical studies. These data will be collectively used for Time and Power predictive analytics and reported in an aggregate fashion.

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. In particular, any deviations from the study 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.

13.4.2 Electronic Data Capture

An electronic data capture (EDC) system will be utilized by study site personnel to transfer study 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, 79 Fifth Avenue, 8th Floor, New York, New York, 10003). This system was designed and is developed and maintained by Medidata 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 study 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 (per Medidata web site) staffed by the outsourced vendor will also be available to respond to site-monitor questions. Contact information for this help desk will be provided during site training.

13.4.3 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 ID number will be visible on each eCRF. At no time should the subject name appear on the eCRFs.

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

13.4.4 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(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within Medidata® Rave.

13.4.5 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 study subject. 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.

13.5 DEVIATIONS FROM THE PROTOCOL

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 PI will report protocol deviations to the IRB as required by the IRB procedures.

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) involves 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. The Investigator reports the protocol amendments implemented without prior Sponsor or IRB approval (i.e. where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study) to the Sponsor as soon as possible.

13.6 RECORD RETENTION, INSPECTION, AND CUSTODY

The PI must maintain all documentation related to the study for three (3) years after site closure (per Korean GCP) and until they receive Sponsor notification. The PI will allow representatives of the Sponsor, MFDS, 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.
Subject medical records will be maintained in a confidential manner. Study reports will not identify subjects by name. These reports may be submitted to MFDS and/or regulatory authorities.

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

14.0 SPONSOR RESPONSIBILITIES

This study is sponsored by Johnson & Johnson Medical Korea Ltd and will be conducted at one site in Korea, under a single protocol approved by the participating site's IRB prior to implementation.

14.1 IRB APPROVAL

The Sponsor requires this Protocol to be submitted to the IRB for initial review and approval before implementation at each site. Additionally, all protocol amendments must be submitted to the IRB for review and approval before implementation.

The site is required to submit a copy of the IRB initial approval, and any subsequent renewals to the Sponsor for filing in the clinical trial's Trial Master File. The site is to maintain the original documentation of the initial approval and renewals in the site's Investigator Site File.

14.2 DATA MANAGEMENT

The Sponsor or designee will perform all data management activities for this clinical investigation. These activities include development and validation of a clinical database, into which all clinical investigation data will be entered. The Sponsor or designee will be responsible for ensuring overall integrity of the data and database.

14.3 INVESTIGATOR TRAINING

Prior to screening subjects for this study, the PI, sub-Investigators, study coordinators, and other designated staff (as applicable) will be provided training on this Protocol, including:

- all general aspects of study administration,
- all study execution, data collection, and procedures in the protocol,
- the EDC application, based on their study role.

14.4 CLINICAL MONITORING

This study will be monitored by the Sponsor to ensure:

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

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, 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 and after their return to the Sponsor; any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the study and mutually 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. These monitoring procedures are characterized in the monitoring plan for this study.

14.5 REGULATORY REQUIREMENTS

This study will be conducted in accordance with MFDS Regulations, including Medical Device Act, ICH Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki (2008), Korean Guidelines for Good Clinical Practice, as well as any other applicable local regulatory requirements.

14.6 SPONSOR TRIAL TERMINATION

The Sponsor may prematurely terminate or suspend the clinical trial for significant and documented reasons. Reasons for premature termination or suspension include, but are not limited to safety, inadequate recruitment, Principal Investigator issues, device-related problems, alignment with business strategy or administrative issues.

In the event of the study being terminated, any enrolled Subjects that have not yet had the ablation procedure would be treated as per their doctor's standard practice. All enrolled Subjects would continue to be cared for by their doctor according to his/her standard of care. No further study-related procedures or data collection would occur.

14.7 INSURANCE

The Sponsor will secure and maintain in full force and effect, throughout the duration of the clinical trial, clinical trial insurance where required in line with national regulations and which will be evidenced by an insurance certificate.

14.8 FINANCIAL AGREEMENT

Funding of this clinical trial will be detailed in a separate Clinical Trial Agreement between the Sponsor and the Institution where the clinical investigation is being conducted and the Principal Investigator (where permitted by the Institution).

14.9 PUBLICATION PLAN

All manuscripts of data obtained from this clinical trial 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 STATISTICAL METHODOLOGY

15.1 STATISTICAL AND ANALYTICAL PLANS

A comprehensive and detailed Statistical Analysis Plan will be finalized prior to database lock and will 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. Confidence intervals will also be provided for procedure-related variables.

15.2 STUDY DESIGN

This is a prospective, single-arm, single-center study in subjects undergoing microwave ablation using the NeuWave Medical's Certus 140™ 2.45GHz Ablation System. Subjects will be followed for up to 36 months following the ablation procedure.

15.3 INTERVAL WINDOWS

Subjects are scheduled for 9 post-ablation visits under this protocol. For summarization of selected endpoints at post-ablation time points, the following windows will be defined around each scheduled visit to identify the corresponding measurement to be summarized for that visit:

- Visit 3 – 1 month (± 14 days) post ablation;
- Visit 4 – 3 months (± 28 days) post ablation;
- Visit 5 – 6 months (± 28 days) post ablation;
- Visit 6 – 9 months (± 28 days) post ablation;
- Visit 7 – 12 months (± 28 days) post ablation;
- Visit 8 – 18 months (± 28 days) post ablation;
- Visit 9 – 24 months (± 28 days) post ablation;
- Visit 10 – 30 months (± 56 days) post ablation; and
- Visit 11 – 36 months (± 28 days) post ablation.

In cases where multiple measurements fall into a given window, the measurement that is closest in time (number of days) to the scheduled measurement will be utilized in all analyses. Subject and site compliance with the protocol specified visit windows will be monitored throughout the study and the final SAP may be revised to expand the windows as necessary so as not to exclude relevant subject measurements that may be near the existing windows.

15.4 PRIMARY AND SECONDARY ENDPOINTS AND ASSOCIATED HYPOTHESES

The primary and secondary endpoints for this study are specified and described in Section 6.2 of this document. Given the single arm nature of this study, no prospective hypotheses are intended to be evaluated; rather this study will be descriptive in nature.

15.5 LEVELS OF SIGNIFICANCE

Given that no hypotheses are to be tested in this study, no levels of significance are specified.

15.6 ANALYSIS SETS

There will be two primary analysis sets:

- The Full Analysis Set will be defined as all subjects in whom the microwave ablation procedure is completed and who provide information on ablation margins for evaluation

of Technical Success and Technique Efficacy. The Full Analysis Set will be the primary analysis population for summary of the primary endpoint and effectiveness-related secondary endpoints.

- The Safety Set will consist of all subjects in whom the microwave ablation procedure is attempted, i.e. started and regardless of whether it was completed as planned or not. The Safety Set will be the primary analysis population for all safety-related endpoints.

Additional analysis sets may be determined to be necessary (e.g. Per Protocol) pending trial progress and will be identified in the SAP as needed.

15.7 SAMPLE SIZE JUSTIFICATION

A sample size of at least 30 subjects is planned for this study. This is a single arm study and as such, the sample size is not statistically powered for the evaluation of a specific hypothesis, but rather is deemed sufficient to provide meaningful information for evaluation of the specified endpoints and will allow for an informed comparison to existing literature on microwave ablation results. The study will continue to enroll subjects until at least 30 subjects have completed the 3-month visit.

15.8 ANALYSES TO BE CONDUCTED

15.8.1 Disposition of Study Subjects

Subject disposition will be summarized using counts and percentages. The number and percentage of subjects consented, included in each analysis set, completed and discontinued will be tabulated along with the specific reasons for discontinuation.

15.8.2 Demographic and Baseline Characteristics

Summary statistics will be provided for patient demographics and pre-operative surgical characteristics for the Full Analysis Set. Medical and surgical history will be summarized with counts and percentages and summary statistics will also be provided for key baseline laboratory measurements as well as baseline ECOG, Child-Pugh, ASA, and VAS pain scores.

15.8.3 Primary and Secondary Endpoint Analyses

The number and percentage of subjects achieving Technical Success, defined as complete tumor ablation with adequate or insufficient ablation margin, based on contrast-enhanced MRI and CT scans immediately following the ablation procedure, will be summarized and an exact 95% confidence interval will be estimated. A similar summary will be provided for Primary Technique Efficacy, defined as complete tumor ablation with adequate or insufficient ablation margin, based on contrast-enhanced MRI and CT scans follow-up at 1 month after the ablation procedure.

Local tumor progression rates at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months will be estimated using the Kaplan-Meier method and 95% confidence intervals will be provided. Only subjects providing an observation at the given time point will be included in the analysis. A similar summary will be provided for the 36-month for overall and progression free survival rates.

Summary statistics as appropriate for continuous or categorical measurements will be provided for all other secondary effectiveness parameters.

15.8.4 Plans for Analysis

Two analyses of study data are planned. The first will occur after 30 subjects have completed the 3-month visit and is intended to provide an initial estimate of device effectiveness for Technical Success as well as to summarize the peri-operative out to 3-month post-operative safety profile of subjects undergoing microwave ablation. There are no plans to use the results of the first analysis for the purpose of stopping the study early. The second analysis will occur after all subjects have completed study participation.

15.8.5 Handling of Missing Data and Dropouts

All summaries will be performed only on subjects undergoing the ablation procedure and only observed data will be summarized. There will be no imputation of data for early terminated subjects or for enrolled subjects who do not provide a measurement at a given visit. Subjects who terminate prior to the 3-month visit will be replaced. Subjects terminating at or after the 3-month visit will not be replaced.

15.8.6 Analysis of Safety

The number and percentage of subjects experiencing adverse events (AEs) will be summarized at the preferred term level using the SIR clinical practice guidelines for event categorization. Summarization of AEs will also be provided by (1) by relationship to study procedure (MWA); (2) by relationship to the device (study devices); and, (3) by maximum severity. Serious AEs will be summarized in a similar manner.

Concomitant procedures and hospital readmission will be summarized with counts and percentages. Summary statistics for laboratory parameters over time may be provided. Post ablation concomitant medications will be listed for all subjects.

15.8.7 Integrated Multi-Study Analysis of Time and Power Data

"Time and Power" data from this study (i.e., how much time and microwave power was applied to a specific lesion, etc.) and the results/outcome of each ablation treatment (i.e., did the treatment results in a complete ablation or not, etc.) will be combined with Time and Power data and ablation outcome date from other studies that use the NeuWave Microwave Ablation Systems. The goal of this Time and Power predictive analysis is to characterize the optimal microwave ablation treatment parameters for specific lesion types, locations, and conditions. All data submitted to and included in this integrated multi-study analysis will be de-identified. Nevertheless, each patient will be asked to give consent to allow his or her data to be submitted for inclusion in this integrated analysis. There is no additional data that will be required for this analysis which is not already collected in this study.

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17.0 DOCUMENT FILING

A copy of all approved versions of the Study Protocol will be kept, by the site, in the Investigator Site File and in the Sponsor Trial Master File.

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