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A Single-Arm, Prospective, Multicenter Study to Evaluate the Safety and Effectiveness of the NeuWave Certus Microwave Ablation System in Chinese Patients with Hepatocellular Carcinoma

NEU_2017_07

Name of investigational medical device	NeuWave Certus Microwave Ablation System and Accessories
Model/specification	NWC2CN1N
Management category of investigational medical device	Class III medical device that needs the approval for clinical trial Y☐ N√ Similar product in same category in China Y√ N☐
Administrative Change 1	Final
Protocol date	06 August 2020
Clinical trial leading institution	Chinese PLA General Hospital
Lead Investigator	Dr. Liang, Ping
Sponsor	NeuWave Medical, Inc.
Agent	Johnson & Johnson Medical (Shanghai) Ltd.

Protocol Approval Form

Protocol Number:	NEU_2017_07
Protocol Title:	A Single-Arm, Prospective, Multicenter Study to Evaluate the Safety and Effectiveness of the NeuWave Certus Microwave Ablation System in Chinese Patients with Hepatocellular Carcinoma
Protocol Date:	06 August 2020

	Name	Signature	Date
Author	[redacted]		

Approvals:

Title	Name	Signature	Date
International Leader Preclinical, Clinical, Medical	[redacted]		
Clinical Franchise Platform Lead			
Medical Affairs Department Head, Senior Director Johnson & Johnson Medical (Shanghai) Ltd.			
BU Regulatory Affairs Head Associate RA Director			
Associate Director, Data Management and Biostatistics			

COMPLIANCE STATEMENT

This study will be conducted in compliance with the Declaration of Helsinki as well as all applicable local regulations.

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SYNOPSIS

Study Title	A Single-Arm, Prospective, Multicenter Study to Evaluate the Safety and Effectiveness of the NeuWave Certus Microwave Ablation System in Chinese Patients with Hepatocellular Carcinoma
Protocol Number:	NEU_2017_07
Control:	Not applicable.
Study Key Objective	The key objective of this study is to evaluate the efficacy and safety of the NeuWave Certus Microwave Ablation System in the treatment of Chinese patients with hepatocellular carcinoma (HCC) a single tumor up to 5 cm or up to 3 tumors no more than 3 cm per tumor.
Number of Study Sites	4 sites
Number of Patients	137 patients, of which 3 patients per each site (n=12) will be part of the run-in phase. This also accounts for a 20% drop out rate.
Study Design	This is a single-arm, prospective, multicenter, study. Individuals who are assessed for microwave (MW) ablation of HCC in accordance with their institution's standard of care (SOC), who meet study entry criteria and sign the informed consent, will be enrolled. The patients will be treated with MW ablation and afterwards followed for up to 36 months after the original ablation procedure to assess efficacy and safety. In addition to the final analysis after all enrolled patients complete the 36-month observation period, a summary of selected endpoints will be provided after all enrolled patients have completed each of the 1-month and 12-month visits. To provide sites with an opportunity to get equal experience in the use of the Certus system, there will 3 patients treated as part of a run-in phase. These patients will only be included in the safety set.

Procedure(s) Description	Patients who have a single HCC tumor up to 5 cm or a maximum of 3 HCC tumors of up to 3 cm per tumor will receive the same procedure: microwave ablation using only the NeuWave Certus Microwave Ablation System. Patients in this study will come to their study site for the ablation procedure. After the ablation procedure, the patient will be observed, which in most cases is expected to be 2 to 3 hours, and afterwards may return home. If the Study Doctor decides it is warranted for patient safety, the patient will remain in the hospital longer. A minimum of one MRI of the liver must be taken at Baseline/Screening to ascertain tumor type, location, and size. (Tumor size will be measured in longest diameter and the diameter that is perpendicular to this longest diameter; tumor size must be measured with at least 2D imaging.) Physicians who are experienced with tumor ablation will do all ablations percutaneously using only the NeuWave Certus Ablation System. During the ablation, patients will be under an anesthesia method as per the institution's SOC. Ultrasound and/or CT scan will be used to guide the probe to the tumor and confirm accurate placement of the probe prior to emitting the microwaves. Within 7 days after ablation, contrast-enhanced MRI will be done to confirm the completion of the ablation procedure. According to the standard practice at each study site, ablation confirmation will be classified as: • complete tumor ablation with adequate margin (A0). • complete tumor ablation with insufficient margin (A1). • incomplete tumor ablation (A2). Over the course of 3 years, patients will return to their study site for post ablation follow-up visits, which will be carried out per the Schedule of Activities (see Table 1 at the end of the Synopsis). The follow-up schedule will be based on the original ablation procedure date. A re-ablation for any reason will not re-start or change the follow-up visit schedule. At every follow-up visit, every patient will be scanned with at least one MRI to see if there are any tumor foci at the edge of the ablation zone, which indicates tumor progression. Repeat microwave ablation (using the Certus Microwave Ablation System only) may be performed for recurrence of target tumor(s) or to achieve complete tumor ablation with adequate margin (A0) of the target tumor(s) if the initial ablation had an insufficient margin, if the treating physician deems appropriate and necessary.

	While repeat ablations for a recurrence may be conducted at any point during the study duration, repeat ablations to correct an ablative margin may only be performed within the first 30 days of the original ablation (by Visit 3).

Study Endpoints	**Efficacy Endpoints:** • Technical Success, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins) based on contrast-enhanced Magnetic Resonance Imaging (MRI) performed up to 7 days following the original ablation procedure. • Technical Efficacy, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins), based on contrast-enhanced MRI scans at 1 month (+/- 7 days) after the original ablation procedure. • Local tumor progression (LTP), evaluated at every visit after the ablation of the target tumor. LTP describes the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up MRI scan has documented adequate ablation and an absence of viable tissue in the target tumor and surrounding ablation margin by using imaging criteria. • Secondary efficacy rate, defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression at any time during study follow up. • Progression-free survival, defined as length of time from the original ablation procedure until any type of disease progression (i.e. local or distant). • Overall-survival, measured from the time of the original ablation procedure to the time of death or last follow-up, if death has not occurred. **Safety Endpoint:** • Adverse events (AEs) and serious adverse events (SAEs) reported at each analysis and cumulatively throughout the entire study period. **Patient Reported Outcomes:** • Pain, as measured by Numeric Pain Rating Scale, before the ablation procedure (measured at Screening Visit), post ablation (within 7 days after ablation]), and at the 1-month follow-up visit.

	• Quality of Life, as measured by EORTC QLQ-C30 and liver-specific EORTC QLQ-HCC18, before the ablation procedure (measured at Screening Visit), post ablation (within 7 days after ablation), and at each follow-up visit. **Health Economics:** • Health economics associated with the ablation procedure, including complete procedure time, ablation time, number of ablations, number and types of probes, change in probe position, number of computed tomography (CT) 、 ultrasound scans performed for probe placement and length of hospital stay.
Inclusion Criteria	• Diagnosed primary or recurrent HCC determined in accordance with the institution's SOC procedure, a single tumor size up to 5 cm or a maximum of 3 tumors up to 3 cm per tumor. Tumor size must be measured with at least 2-dimensional (2D) imaging. • Scheduled for microwave ablation of the liver. • Performance status 0-2 (Eastern Cooperative Oncology Group classification). • Functional hepatic reserve based on the Child-Pugh score (Class A or B). • Give voluntary, written informed consent to participate in this study and willing to comply with study-related evaluation and procedure schedule. • At least 18 years of age.
Exclusion Criteria	1. ASA score ≥ 4. 2. Active bacterial or fungal infections which are clinically significantly. 3. Chemotherapy or radiation therapy for HCC performed within 30 days prior to the study procedure. 4. Patient with implantable pacemakers or other electronic implants. 5. Planned/ scheduled liver surgery. 6. Platelet count ≤ 50 × 10^9/L. 7. Patients with uncorrectable coagulopathy at time of screening based on investigator judgement. Severe blood

	coagulation dysfunction (bleeding tendency, prothrombin time [PT] was greater than normal control for 3~5 seconds, platelet count [PLT] was less than $50x10^9$/L, and the international normalized ratio [INR] was greater than 1.5). 8. Patient with renal failure and on renal dialysis. 9. Scheduled concurrent procedure other than MW ablation in the liver. 10. Pregnant or breast feeding. 11. Physical or psychological condition which would impair study participation. 12. Participation in any other interventional clinical study within 1 month before screening and concurrently during the study. 13. The patient is judged unsuitable for study participation by the investigator for any other reason.
Study Duration	Planned recruitment period: approximately 8 months for 137 patients at 4 participating sites. Follow-up period: 36 months.
Safety	Patients will be assessed for all AEs and SAEs for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported.
Statistical Methods	Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum. Confidence intervals will also be provided for procedure-related variables. The number and percentage of tumors achieving Technical Success will be summarized and a 95% confidence interval will be estimated. Technical Success will be evaluated based on the margin achieved after the first ablation and prior to any repeat ablations within the first 7 days. A similar summary will be provided for Technical Efficacy. This endpoint will be based on the scan obtained at Visit 3 and will count as successes patients with A0 or A1 margins in that scan and who

	did not have an A2 margin since the Visit 2B scan. Additionally, if a patient received a repeat ablation for correcting a margin (to go from A1 to A0) within the first 30 days, this will also count as a success. Patients with repeat ablations to correct an A2 margin from Visit 2B to Visit 3 will not count as success for Technical Efficacy. The number and percentage of tumors with A0 and A1 margins will be presented as a sub-categorization within each presentation of Technical Success and Technical Efficacy, as well as a summarization for the number and reasons for repeat ablations through Visit 3. 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. Any repeat ablation required after Visit 3 (Month 1) will be identified as an instance of local tumor progression. A similar summary will be provided for the 36-month overall and progression-free survival rates. The number and percentage of patients experiencing AEs will be summarized at the preferred term level using the Society of Interventional Radiology (SIR) clinical practice guidelines for event categorization. A similar summary will be provided for device-related AEs, procedure-related AEs, all SAEs, device-related SAEs, and procedure-related SAEs. Three analyses of study data are planned. The first will occur after all enrolled patients have completed the 1-month visit and is intended to provide an initial estimate of device effectiveness for Technical Success as well as to summarize the peri-operative until 1-month post-ablation safety profile of patients undergoing MW ablation. A similar analysis will occur after all patients have completed the 12-month visit and will include a summary of local tumor progression rates as well as safety through one year. There are no plans to use the results of either analysis for the purpose of stopping the study early. The third analysis will occur after all patients have completed study participation.

Table 1: Schedule of Activities

Visits	**Screening**	**Ablation**	**Post ablation**	**1 month post ab.**	**3 months post ab.**	**6 months post ab.**	**9 months post ab.**	**1 year post ab.**	**18 months post ab.**	**2 years post ab.**	**30 months post ab.**	**3 years post ab.**	**USV[12]**
	Visit 1	Visit 2A	Visit 2B	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	
Interval Windows: Activities	within 14 d prior to ablation	Day 0	within 7 d after ablation	1 month (+/- 7 d)	3 months (+/- 7 d)	6 months (+/-14 d)	9 months (+/-14 d)	12 months (+/-14 d)	18 months (+/-28 d)	24 months (+/-28 d)	30 months (+/-28 d)	36 months (+/-28 d)	N/A
Informed consent	X												
Demographic information	X												
Medical/surg/rad history[1]	X												
Inclusion / exclusion	X	X											
Pain score (NPRS)	X		X	X									
EORTC QLQ-C30/HCC18	X		X	X	X	X	X	X	X	X	X	X	
MRI scan (liver)	X[2]		X[3]	X	X	X	X	X	X	X	X	X	
CT scan of the liver	O[2]	X[4]											
Ultrasound (liver)	O[2]	X[4]											
Pregnancy test[5]	X												
Laboratory tests[6]	X		X	X	X	X	X	X	X	X	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[7]		X											
Device accountability		X											

Visits	**Screening**	**Ablation**	**Post ablation**	**1 month post ab.**	**3 months post ab.**	**6 months post ab.**	**9 months post ab.**	**1 year post ab.**	**18 months post ab.**	**2 years post ab.**	**30 months post ab.**	**3 years post ab.**	**USV**[12]
	Visit 1	Visit 2A	Visit 2B	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	
Interval Windows: Activities	within 14 d prior to ablation	Day 0	within 7 d after ablation	1 month (+/- 7 d)	3 months (+/- 7 d)	6 months (+/-14 d)	9 months (+/-14 d)	12 months (+/-14 d)	18 months (+/-28 d)	24 months (+/-28 d)	30 months (+/-28 d)	36 months (+/-28 d)	N/A
Length of hospital stay			X										
Complete tumor ablation evaluation			X	X									
LTP evaluation[8]				X	X	X	X	X	X	X	X	X	
Progression-free survival[8]				X	X	X	X	X	X	X	X	X	
Concomitant meds[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures[10]			X	X	X	X	X	X	X	X	X	X	X
AEs and SAEs[11]		X	X	X	X	X	X	X	X	X	X	X	X

Symbol: "O" means that ultrasound and computed tomography (CT) scans are optional for Screening.

Abbreviations: ab. = ablation; AEs = adverse events; ASA = American Society of Anesthesiologists; CT = computed tomography; d = days; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HCC = hepatocellular carcinoma; LTP = local tumor progression; meds = medications; MRI = Magnetic Resonance Imaging; NPRS = numeric pain rating scale; rad = radiation; SAEs = serious adverse events; SOC = standard of care; surg = surgical; USV = unscheduled visit.

Notes:

1. Review and collect medical, surgical, and radiation histories, including alcohol consumption and hepatitis, if applicable. Note: HCC diagnosis does not need to be reported as medical history.

2. At minimum, an MRI of the liver must be taken at Baseline/Screening (per each study site's SOC) to ascertain tumor type, location, and size (measured in longest diameter and the diameter that is perpendicular to this longest diameter). Tumor size must be measured with at least 2D imaging. The MRI must

be taken within 14 days prior to ablation (Visit 2A). Ultrasound and/or CT are optional.

3. An MRI must be taken within 7 days following the ablation procedure.
4. Ultrasound and/or CT will be used to guide the probe into place and confirm accurate placement of the probe prior to ablation . For ultrasound, a video of the ablation may be submitted to the Sponsor.
5. Serum pregnancy test, for women of childbearing potential only, must be performed within 14 days prior to ablation (Visit 2A); otherwise the test must be repeated and available prior to ablation.
6. All laboratory tests must be performed within 14 days prior to ablation (Visit 2A), otherwise the test(s) must be repeated and available prior to ablation. For follow-up Visits 3 to 11, the laboratory tests may be done within 7 days prior to the respective visit. The laboratory tests are: coagulation (PT, APTT, INR); liver function (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, and total protein); renal function (Urea, creatinine and electrolytes (sodium, potassium and chloride); complete blood count (differential cell count and platelet count); and, alpha-fetoprotein.
7. Procedure details include, but are not limited to, the following: complete procedure time; ablation time; anatomical location of ablation; number of probe placement attempts; number of ablations, ablation maximum power and time used for each probe and ablation; guidance method used; number of ultrasound scans performed for probe and margin assessment. While repeat ablations for a recurrence may be conducted at any point during the study duration, repeat ablations to correct an ablative margin may only be performed within the first 30 days of the original ablation (by Visit 3). Procedure details should be collected for all re-ablations, if applicable.
8. Local tumor progression (LTP) and Progression-free survival will be evaluated by a study physician based on MRI imaging. Progression-free survival may be reported by a patient's treating oncologist, if different than the study physician. All MRI scans are to be submitted to the Sponsor. If there is a progression, the study physician should specify if the progression is of the original target tumor, a new HCC tumor in the liver or a distant metastasis.
9. Include all relevant medications taken within 14 days prior to prior to ablation (Visit 2A) and taken throughout the study. Relevant medications include chemotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, and those used for hepatitis (if concurrently treating). Note: Elements that comprise anesthesia do not require reporting into the clinical database.
10. Record only relevant concomitant procedures.
11. Patients will be assessed for all AEs and SAEs for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported.
12. Record reason for unscheduled visit, as well as all AEs and SAEs if within 30 days after an ablation procedure, and only SAEs if after 30 days post an ablation procedure, and any updates to the relevant concomitant medications and relevant concomitant procedures.

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GLOSSARY

Acronyms	Terms
2-D	2-dimensional
AE	Adverse event
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
NMPA	National Medical Products Administration
CHU	Complaint handling unit
CT	Computed tomography
DFS	Disease-free survival
EC	Ethics committee
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
FDA	Food and Drug Administration
GCP	Good clinical practices
GGT	Gamma-glutamyl transpeptidase
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HBV	Hepatitis B virus
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LTP	Local tumor progression
MRI	Magnetic resonance imaging
MW	Microwave

Acronyms	Terms
NPRS	Numeric pain rating scale
OS	Overall survival
PI	Principal investigator
PDM	Power distribution module
PLT	Platelet count
PT	Prothrombin time
QLQ	Quality of life questionnaire
RF	Radiofrequency
SAE	Serious adverse event
SAP	Statistical analysis plan
SIR	Society of Interventional Radiology
SOC	Standard of care
SOP	Standard operating procedure
US	United States
USV	Unscheduled visit

1. SPONSOR INFORMATION

(1) Name of Sponsor:

NeuWave Medical, Inc.

3529 Anderson Street

Madison, Wisconsin, 53704, USA

(2) Contact of Sponsor:

[redacted]

(3) Related qualification documents of Sponsor:

The CE certification is available as a separate attachment.

(4) Name, address, contact and related qualification documents of agent:

[redacted]

The business license is available as a separate attachment.

2. LIST OF CLINICAL TRIAL INSTITUTIONS AND INVESTIGATORS

Code of clinical trial institution	Name of clinical trial institution	Investigator	Title
01069*	Chinese PLA General Hospital	Ping Liang	Director
01065#	Sun Yat-sen University Cancer Center	Jinhua Huang	Director
01066#	The First Affiliated Hospital, Sun Yat-sen University	Xiaoyan Xie	Director
01067#	Renji Hospital, Shanghai Jiao Tong University School of Medicine	Bo Zhai	Director

* Information of leading site and principal investigator

Information of co-site and co-principal investigator.

3. OBJECTIVE AND CONTENTS OF CLINICAL TRIAL

3.1. Objective of Clinical Trial

The key objective of this study is to evaluate the efficacy and safety of the NeuWave Certus Microwave Ablation System in the treatment of Chinese patients with a single hepatocellular carcinoma (HCC) tumor up to 5 cm or a maximum of 3 HCC tumors up to 3 cm per tumor.

3.2. Contents of Clinical Trial

This single-arm, prospective, multicenter study will enroll approximately 137 Chinese patients who have a single HCC tumor up to 5 cm or a maximum of 3 HCC tumors up to 3 cm per tumor. All qualified patients at the 4 participating study sites will receive the same procedure: microwave ablation using only the NeuWave Certus Microwave Ablation System. Patients in this study will come to their study site for the ablation procedure. After the ablation procedure, the patient will be observed, which in most cases is expected to be 2 to 3 hours, and afterwards may return home. If the Study Doctor decides it is warranted for patient safety, the patient will remain in the hospital longer. All patients will be required to return to their study site for 9 follow-up visits over a period of 36 months to assess efficacy and safety.

Efficacy will be assessed by using contrast-enhanced Magnetic Resonance Imaging (MRI) to verify that the patient's tumor was completely ablated and to measure the size of the margin around the ablated tumor. When the MRI scans are done within 7 days after the ablation, Technical Success is assessed. When the MRI scans are done 30 days (± 7 days) after ablation, Technical Efficacy is assessed. At every follow-up visit, the patient will be scanned with at least one MRI to see if there are any tumor foci at the edge of the ablation zone, which indicates local tumor progression (LTP). These MRIs will also serve as the basis for determining progression-free survival, defined as length of time from the original ablation procedure until any type of disease progression (i.e. local or distant). Another valuable endpoint during the 36-month follow-up period will be overall survival, measured from the time of the original ablation procedure to the time of death or last follow-up if death has not occurred.

Patients will be assessed for all AEs and SAEs for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported and assessed.

4. BACKGROUND INFORMATION OF CLINICAL TRIAL

4.1. Introduction to the Condition

4.1.1. Explanation for the Condition

Primary liver cancer or 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 HCC 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.

HCC is the sixth most common cancer worldwide with approximately 782,000 new cases and 745,000 deaths annually.[1] and the third most common cause of death from cancer (598,000 deaths annually).[2] More recently in China, liver cancer is the second major cause of cancer deaths, with a mortality rate of 26.26 per 100,000 (males: 37.55 and females: 14.45 per 100,000), accounting for 19.33% of all sites of cancers. Accordingly, the estimated annual incident cases and deaths of liver cancer are 360,000 and 350,000, respectively.[3]

Surgical resection is the reference standard for treatment of HCC, however only a small proportion of HCC patients are candidates because of disease progression, anatomical location, and/or poor liver function. In these cases, imaging-guided percutaneous ablation can be better options. It features significant advantages including that it's minimally invasive, safe, easy to operate, easy to implement repeatedly, and has relatively low cost.[4] Recurrence of HCC is common in patients who have undergone surgical resection; for those patients, the image-guided methods are easier and safer option than surgical resection. Indeed, image guided methods have been widely used in China.

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. In 2011, Chinese experts published their consensus on ablation for HCC.[3] In this consensus, local ablation therapy is considered as one of the radical treatments of small HCC.

Microwave Ablation to Treat HCC in China

The largest clinical experience using MW ablation to treat HCC comes from China, in part due to early adoption of MW ablation systems available only in Asia. That multicenter study of 1007 patients with primary liver cancer showed a technical success of 97.1% (1276/1363) and a local tumor progression rate of 5.9% (78/1363) with a mean follow-up time of 17.3 months (range, 3-68.9 months). The 1-, 3- and 5-year overall survival rates were 91.2%, 72.5% and 59.8%, respectively.[5]

A retrospective study of MW ablation as a first-line treatment for HCC evaluated the long-term outcomes and prognostic factors of 221 consecutive patients receiving MW ablation in Renji Hospital (Shanghai) between October 11, 2010 and December 31, 2013 were enrolled. Technique effectiveness was evaluated 1-month post-ablation. Initial complete ablation was found in 201 (90.95%) patients, secondary technique effectiveness in 8 (3.62%) patients, and the remaining 12 (5.43%) patients suffered from incomplete ablation after 2 sessions of MW ablation. No patients died within 30 days post ablation. Major complications occurred in 8 (3.8%) patients. It was concluded that MW ablation provides high technique effectiveness rate and is well tolerated in patients with HCC as a first-line treatment.[6]

Literature Review

Pre-clinical and clinical data has shown that MW 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).[7]

Based on a review of the current literature on clinical MW ablation, collectively[3], the studies demonstrate that microwave (MW) ablation is a safe and effective therapy for tumors in the liver, lung, kidney and bone when compared with the current clinical standard, RF ablation. In particular, they demonstrate that MW ablation is associated with high rates of technical success, low anesthesia complication rates, low rates of local recurrence and good long-term survival. In addition, the studies illustrate several advantages of MW ablation, including uniform cell kill within ablation zones, multiple-antenna capability, and improved perivascular ablation. The treatments were performed using multiple different MW 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 MW 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.

4.1.2. Therapeutic Option and Prognosis

Microwave Ablation Compared with Hepatic Resection

Shibata et al[8] 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 MW 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 MW ablation group. Recently, Zhang et al[9] 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 (overall survival [OS] and disease-free survival [DFS] were similar between groups).

Shi et al[10] compared MW ablation and surgical resection for treating patients with HCC within Milan criteria. For solitary tumors $\leq$ 3 cm, 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. Chong et al[11] conducted a retrospective study comparing MW ablation with liver resection and found that with propensity score matching of the two groups that resulted in 63 matched pairs, liver resection had better overall survival and disease-free survival in patients with albumin-bilirubin grade 1. However,

MW ablation showed a significantly better overall survival and a trend towards better disease-free survival in patients with albumin-bilirubin grade 2 or 3.

Adoption of MW ablation systems has previously been limited by technical problems associated with suboptimal power handling, large antenna diameter, antenna shaft heating and unpredictable heating patterns. Despite these limitations, the results of clinical MW ablation studies have historically compared favorably with those of RF ablation. In a recent meta-analysis, RF ablation and MW ablation had similar 1- to 5-year overall survival, disease-free survival, local recurrence rate, and adverse events (AEs). However, MW ablation demonstrated a superior 6-year overall survival.[12] As MW ablation technology has advanced, and our understanding of MW energy delivery has improved, MW ablation systems have become increasingly utilized in interventional oncology practices.

4.2. Application of Investigational Product

Thermal ablation is increasingly utilized in the treatment of primary and metastatic liver tumors, both as curative therapy and as a bridge to transplantation. Recent advances in high-powered MW ablation systems have allowed physicians to realize the theoretical heating advantages of MW energy compared with other ablation modalities. As a result, there is a growing body of literature detailing the effects of MW energy on tissue heating, as well as its effect on clinical outcomes.[13]

Multiple-Antenna Microwave Ablation

Several reports have demonstrated that multiple-antenna MW ablation is safe and improves treatment efficacy. Multiple antennas were used in the studies by Simon et al[14] and Meredith et al[15] described above. In addition, Yu et al[16] 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.

Microwave Ablation with a Gas-Cooled System

The results of HCC treatment with a high-power, gas-cooled, multiple antenna-capable MW device were retrospectively reviewed by Ziemlewicz et al.[17] A total of 107 HCCs in 75 patients were treated via percutaneous approach. All procedures were performed with a single MW system (Certus) with one to three 17-gauge antennas. Primary technique effectiveness rate was 91.6% (98 of 107) overall. Ziemlewicz concluded that treating HCC with a gas-cooled, multiantenna-capable MW ablation device is safe, with promising treatment effectiveness.

4.3. Product Registration and Reason for Clinical Trial Registration in China

The Certus Microwave Ablation System and Accessories have been 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 tumors. Additional, but less common uses have been nerve ablation and the

ablation of soft tissue tumors in bone.

This device has not been used in general ablation procedures in the Chinese population. Therefore, the clinical study is designed to support the registration of the device in China.

5. FEATURES, STRUCTURAL COMPOSITION, OPERATION PRINCIPLE, MECHANISM OF ACTION, AND STUDY POPULATION

5.1. Features

5.1.1. Design Features of Study Product

Neuwave Medical's Certus Microwave Ablation System and Accessories consists of Software version 3.0.X and the accessories NEUWAVE Certus PR, NEUWAVE Certus LK, and NEUWAVE Certus SR ablation probes. Several accessories designed to allow for the mechanical interfacing of the Power Distribution Module (PDM) to a variety of vendors' CT (computed tomography) 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 system uses a CO_2 cooling system where all other MW 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 system does not introduce new hazards or intended uses.

The Certus Microwave Ablation System and Accessories are intended to ablate/coagulate soft tissue using microwaves in the United States. The Certus Microwave Ablation System and Accessories are general purpose thermal ablation tools used by physicians to ablate soft tissue tumors in a wide variety of tissue and disease states in the United States.

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

5.2. Study Population

The study population will include 137 Chinese patients with a single HCC tumor up to 5 cm or a maximum of 3 HCC tumors up to 3 cm per tumor.

6. INDICATIONS AND CONTRAINDICATIONS, PRECAUTIONS

6.1. Indications

The Certus Microwave Ablation System and Accessories form a Microwave Ablation System, which is intended to ablate/coagulate soft tissue. The Certus Microwave Ablation System and Accessories are general purpose thermal ablation tools used by physicians to ablate soft tissue

tumors in a wide variety of tissue and disease states. The most common applications by clinicians have been the ablation of liver, kidney and lung tumors. Additional, but less common uses have been the ablation of soft tissue tumors in bone and nerve ablation.

6.2. Contraindications

The Certus 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 MW power.
- Use on the central nervous system.
- Endometrial applications.

6.3. Precautions

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

Important: Probe temperatures are highly dependent on tissue variables such as perfusion and vasculature. Probe temperatures are likely to vary from procedure to procedure based on these tissue variables. These temperature variations do not, by themselves, indicate a malfunctioning probe or system.

Electrosurgical/electrocautery devices may interfere with the Certus system and cause system errors. Ensure that all Certus probes are removed from the patient prior to using electrosurgical/electrocautery devices.

Use only Certus Ablation Probes from NeuWave Medical with the Certus Ablation System. Probes from other manufacturers may cause patient injury or fail to function properly.

The Certus system uses a CO_2 cooling system where all other MW 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 system does not introduce new hazards or intended uses.

This product should only be used by clinicians and staff properly trained in the use of the technology and its associated warnings and cautions.

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

7. OVERALL DESIGN

7.1. Trial Design

This is a single-arm, prospective, multicenter study. Individuals who are assessed for MW ablation of HCC in accordance with their institution's standard-of-care (SOC), who meet study entry criteria and sign the informed consent will be enrolled. The patients will be treated with MW ablation and afterwards will be followed for up to 36 months after the ablation procedure to assess safety and ablation outcomes. In addition to the final analysis after all enrolled patients complete the 36-month observation period, a summary of selected endpoints will be provided after all enrolled patients have completed each of the 1-month and 12-month visits.

7.1.1. Trial Objective

The key objective of this study is to evaluate the efficacy and safety of the NeuWave Certus Microwave Ablation System in the treatment of Chinese patients with a single HCC tumor of up to 5 cm or a maximum of 3 HCC tumors of up to 3 cm per tumor.

7.1.2. Trial Endpoints

Efficacy Endpoints

The efficacy endpoints are defined, as follows:

- Technical Success, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins) based on contrast-enhanced MRI performed up to 7 days following the original ablation procedure.
- Technical Efficacy, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins), based on contrast-enhanced MRI scans at 1 month (+/- 7 days) after the original ablation procedure.
- Local tumor progression (LTP), evaluated at every visit after the ablation of the target tumor(s). LTP describes the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up MRI scan has documented adequate ablation and an absence of viable tissue in the target tumor and surrounding ablation margin by using imaging criteria.
- Secondary efficacy rate, defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression at any time during study follow up.
- Progression-free survival, defined as length of time from the original ablation procedure until any type of disease progression (i.e. local or distant).
- Overall survival measured from the time of the original ablation procedure to the time of death or last follow-up if death has not occurred.

Safety Endpoint

The safety endpoint is the rate of AEs and SAEs reported at each analysis and cumulatively throughout the entire study period.

Patient Reported Outcomes:

- Pain, as measured by Numeric Pain Rating Scale, before the ablation procedure (measured at Screening Visit), post ablation (within 7 days after ablation]), and at the 1-month follow-up visit.
- Quality of Life, as measured by EORTC QLQ-C30 and liver-specific EORTC QLQ-HCC18, before the ablation procedure (measured at Screening Visit), post ablation (within 7 days after ablation), and at each follow-up visit.

Health Economics:

- Health economics associated with the ablation procedure, including complete procedure time, ablation time, number of ablations, number and types of probes, change in probe position, number of computed tomography (CT) and ultrasound scans performed for probe and margin assessment, and length of hospital stay.

7.1.3. Trial Method Selection and Its Rationale

This is a single-arm, prospective study. As such, there is no randomization or control groups. Individuals who are assessed for MW ablation of HCC in accordance with their institution's standard of care (SOC), who meet study entry criteria and sign the informed consent will be enrolled. Because it is a prospective study, selection bias may be reduced.

7.1.4. Measures to Reduce and Avoid Bias

There will be no central reviewer, however, all MRI scans and the ultrasound video taken on the day of ablation should be sent to the Sponsor.

The study related data will be recorded in the original Medical Records and reviewed during the monitoring process. Proper Training for the investigators will be planned to ensure all investigators have equal adequate experience with the device prior to commencing enrollment at their site. In addition, all sites will treat a minimum of 3 patients each, as part of the roll-in phase, which will only be included in the safety set. This is intended to reduce any operational bias due to learning curve.

The investigator should communicate further with the patients to improve the patient compliance. This will help to reduce the informational bias.

7.1.5. Selection of Patients

1) Inclusion criteria

- Diagnosed primary or recurrent HCC determined in accordance with the institution's SOC procedure, single tumor size up to 5 cm or a maximum of 3 tumors up to 3 cm per tumor. Tumor size must be measured with at least 2-dimensional (2D) imaging.
- Scheduled for MW ablation of the liver.
- Performance status 0-2 (Eastern Cooperative Oncology Group classification).
- Functional hepatic reserve based on the Child-Pugh score (Class A or B).
- Give voluntary, written informed consent to participate in this study and willing to comply with the study-related evaluation and procedure schedule.
- At least 18 years of age.

2) Exclusion criteria

- ASA score $\geq$ 4.
- Active bacterial or fungal infections which are clinically significantly.
- Chemotherapy or radiation therapy for HCC performed within 30 days prior to the study procedure.
- Patient with implantable pacemakers or other electronic implants.
- Planned/ scheduled liver surgery.
- Platelet count $\leq 50 \times 10^9$/L.
- Patients with uncorrectable coagulopathy at time of screening based on investigator judgement. Severe blood coagulation dysfunction (bleeding tendency, prothrombin time [PT] was greater than normal control for 3~5 seconds, platelet count [PLT] was less than $50x10^9$/L, and the international normalized ratio (INR) was greater than 1.5).
- Patient with renal failure and on renal dialysis.
- Scheduled concurrent procedure other than MW ablation in the liver.
- Pregnant or breast feeding.
- Physical or psychological condition which would impair study participation.
- Participation in any other interventional clinical study within 1 month before screening and concurrently during the study.
- The patient is judged unsuitable for study participation by the investigator for any other reason.

3) Criteria of Sponsor's Discontinuation of the Trial

The Sponsor has the right to terminate the study early for a single site, multiple sites or all sites temporarily or permanently. Reasons may include, but are not limited to: safety issue or ethical issue, inaccurate or incomplete data record, non-compliance or dissatisfactory quality or quantity of the recruited patients. Health authorities also have the right to terminate a study.

This study does not require a Data Safety Monitoring Board.

Other criteria:

Patients may be withdrawn if any of the following complications or adverse situations occur:

- The patient experiences a major complication, which 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 (Society of Interventional Radiology [SIR] classifications C to E).
- The patient requires a blood transfusion or interventional drainage procedure.

Flow of Sponsor's Discontinuation of the Trial:

If this study is terminated or discontinued early, the Sponsor or its representative will inform the investigator/affiliated unit and regulatory authority of the termination of the study and the reasons for the termination or discontinuation, according to the applicable requirements. The Sponsor or investigator/affiliated unit should also inform ECs and include the reasons for termination or discontinuation, according to the applicable requirements. In addition, all unused study devices and other study materials should be returned according to the Sponsor's study procedures.

Study/treatment termination and patient discontinuation criteria and procedures

In accordance with the current revision of the Declaration of Helsinki, a patient has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. Should a patient (or patient's legally authorized guardian/representative) decide to withdraw, 1) all data collected up to the point of withdrawal will be considered for analysis; and 2) all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. The primary reason for early withdrawal will be recorded on the electronic case report form (eCRF). The criteria for withdrawal of patients from the study include, but are not limited to, the following:

Withdrawal of consent**:** Any method of contact with the patient in which the patient's states that he or she no longer wants to participate in the study-specific activities constitutes withdrawal of consent from participation in the study. This decision must be "self-determination" and should be documented in the eCRF; or, the investigator may determine the withdrawal of patients from the study according to reasonable medical judgement;

Adverse event**:** The AE or SAE may not cause the patients to discontinue the study. If the investigator decides to withdraw a patient from the study, this patient must be followed up, until the AE is resolved or until the stable clinical endpoint is reached;

Death**:** The cause of death will be documented.

Lost-to-follow-up**:** All patients should be able to participate in all scheduled clinical follow-ups, providing the appropriate contact information. If a patient can't return to undergo the scheduled

clinical visit, attempts to contact the patient by phone should be done for 3 times to ask the patient to participate in all scheduled clinical follow-ups. Each attempt to contact should be recorded in the source document. If the patient makes no response to all three times of telephone contact, the investigator must send a registered mail to the patient. If the patient makes no response to the registered mail and makes no further contact, the patient is considered lost-to-follow-up and the respective eCRF will be completed.

Procedure for Patient's Discontinuation from the Study:

The patients must return for all follow-up visits as specified at the end of the synopsis in Table 1: Schedule of Activities. If the patient is withdrawn from the study early, the reasons for termination will be documented in the source document and site files and submitted via the eCRF.

Patients withdrawn from the study early will be included in the analysis of results, however, no new patients will be recruited to replace the patients withdrawn from the study as a 20% attrition rate has already been considered in the current sample size.

4) Enrollment

Patients will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process.
- It is determined by the investigator that the patient meets all inclusion criteria and does not meet any exclusion criteria.

No procedures related to the study and which are not SOC should be conducted prior to signing the informed consent.

5) Expected overall duration of clinical trial and reasons for determination

The expected overall duration is approximately 65 months, including the time that each site's Ethics Committee takes to approve the trial protocol, institution contract sign-off, Human Genetic Material Office approval, duration of patient enrollment, duration of follow-up, time for data management, statistical analysis, and time to write, review and approve the clinical study report.

6) Expected duration of participation of each patient

The duration of each patient's participation in the study will be around 37 months (about 1 month for Screening and 36 months for follow-up). The follow-up schedule will be based on the original ablation procedure date. A re-ablation for any reason will not change or extend the follow-up visit schedule.

7) Number of patients required for clinical trial

This study will include 137 patients, of which 3 patients per site (n=12) will be part of the run-in phase. This is a single-arm study, and hence there will be no randomization of patients. See Section 8.2 "Calculation of Sample Size" for the basis for selecting this sample size.

7.1.6. Efficacy Evaluation Method

1) Description of efficacy parameters

The efficacy endpoints and their definitions are the following:

- Technical Success, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins) based on contrast-enhanced MRI, performed up to 7 days following the original ablation procedure.
- Technical Efficacy, defined as a combination of A0 ablations (complete tumor ablation with a surrounding 5 mm margin) and A1 ablations (complete tumor ablation with inadequate margins), based on contrast-enhanced MRI scans at 1 month (+/- 7 days) after the original ablation procedure.
- Local tumor progression (LTP), evaluated at every visit after the ablation of the target tumor(s). LTP describes the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up MRI scan has documented adequate ablation and an absence of viable tissue in the target tumor and surrounding ablation margin by using imaging criteria.
- Secondary efficacy rate, defined as the percentage of tumors that have undergone successful repeat ablation following identification of local tumor progression at any time during study follow up.
- Progression free survival, defined as length of time from the original ablation procedure until any type of disease progression (i.e. local or distant).
- Overall survival measured from the time of the original ablation procedure to the time of death or last follow-up if death has not occurred.

2) Selection of method and time to evaluate, record, and analyze the efficacy parameters

The primary effective parameters in this study will be assessed by the investigator(s) at each site based on examining image data.

7.1.7. Safety Evaluation Method

1) Description of safety parameters

The safety parameters in this study are all AEs and SAEs for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported and assessed. The safety endpoint is the rate of AEs and SAEs reported at each analysis and cumulatively throughout the entire study period.

2) Selection of method and time to evaluate, record, and analyze the safety parameters

Patients will be assessed for all AEs and SAEs for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported. The safety parameters are recorded on the e-CRF according to the investigator's record, medical record, and all other related source documents, which are collected at each follow-up visit.

7.2. Study Process

7.2.1. Study Flowchart

Refer to Table 1: Schedule of Activities, which may be found at the end of the Protocol Summary.

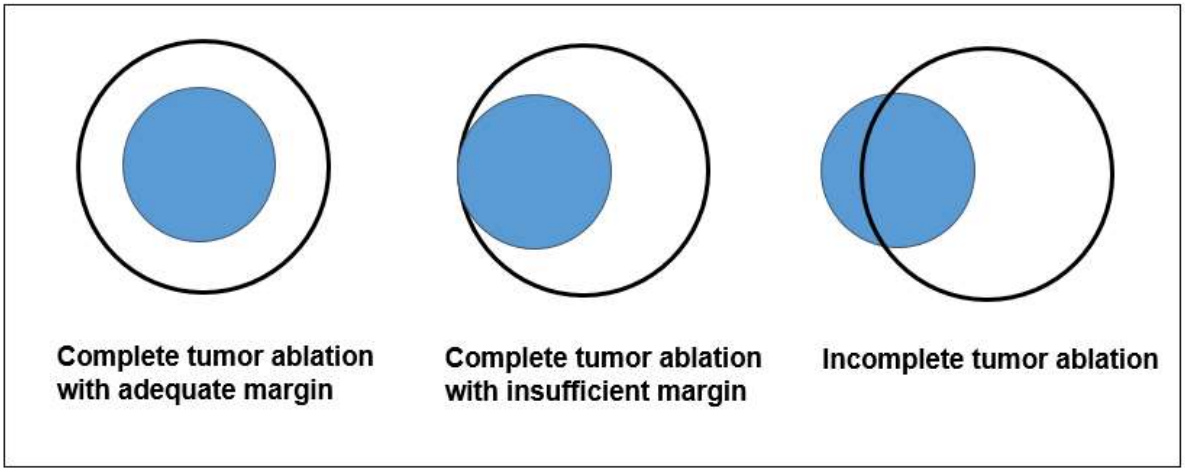
7.2.2. Procedure Description

Patients who have who have a single HCC tumor up to 5 cm or a maximum of 3 HCC tumors of up to 3 cm per tumor will receive the same procedure: microwave ablation using only the NeuWave Certus Microwave Ablation System. Patients in this study will come to their study site for the ablation procedure. After the ablation procedure, the patient will be observed, which in most cases is expected to be 2 to 3 hours, and afterwards may return home; If the Study Doctor decides it is warranted for patient safety, the patient will remain longer.

A minimum of one MRI of the liver must be taken at Baseline/Screening to ascertain tumor type, location, and size. (Tumor size will be measured in longest diameter and the diameter that is perpendicular to this longest diameter; tumor size must be measured with at least 2D imaging.) Physicians who are experienced with tumor ablation will do all ablations percutaneously using only the NeuWave Certus Ablation System. During the ablation, patients will be under an anesthesia method as per the institution's SOC. Ultrasound and/or CT scan will be used to guide the probe to the tumor and confirm accurate placement of the probe prior to emitting the microwaves.

Within 7 days after ablation, contrast-enhanced MRI will be done to confirm the completion of the ablation procedure. According to the standard practice at each study site, ablation confirmation will be classified as:

- Complete tumor ablation with adequate margin (A0).
- Complete tumor ablation with insufficient margin (A1).
- Incomplete tumor ablation (A2).



Over the course of 3 years, patients will return to their study site for post ablation follow-up visits, which will be carried out per the Schedule of Activities (see Table 1 at the end of the Synopsis). At every follow-up visit, the patient will be scanned with at least one MRI to see if there are any tumor foci at the edge of the ablation zone, which indicates local tumor progression (LTP). These MRIs will also serve as the basis for determining progression-free survival, defined as length of time from the original ablation procedure until any type of disease progression (i.e. local or distant).

Microwave ablation (using the Certus Microwave Ablation System only) may be performed for recurrence of target tumor(s) or to achieve complete tumor ablation with adequate margin (A0) of the target tumor(s) if the initial ablation had an insufficient margin, if the treating physician deems appropriate and necessary. While repeat ablations for a recurrence may be conducted at any point during the study duration, repeat ablations to correct an ablative margin may only be performed within the first 30 days of the original ablation (by Visit 3).

7.2.3. Standard Operating Procedures of Medical Device

According to Instructions For Use (IFU) and technical manual of the product, the requirements for the use of study product are as follows:

a. Indications and scope of application:

The NeuWave Certus Microwave Ablation System is indicated for the ablation (coagulation) of soft tissue. The NeuWave Certus Microwave Ablation System is not indicated for use in cardiac procedures. The system is designed for facility use and should only be used under the orders of a physician

b. Recommended operating mode for the Certus system:

Physicians who are experienced with tumor ablation will do all ablations percutaneously

using only the NeuWave Certus Ablation System. During the ablation, patients will be under an anesthesia as per the institution's SOC. 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 or CT scan guidance, a small probe is inserted percutaneously into the tumor.

The ablation will be performed with a single high-powered, gas-cooled, multiple antenna–capable MW system (NeuWave Medical's Certus Ablation System and Accessories) 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 the ablation 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 may 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 tumors ≥ 2 cm.

The Certus Ablation System rests on a cart that contains the MW power amplifiers and cooling system. The user interface for the Certus Ablation System is a system display to access all controls and settings. When ready to begin the procedure, the display will be used to select the tissue locations in which probes will be inserted during the procedure.

Target ablation involves placing a probe into a substantial target and then ablating for up to several minutes until the target tissue is necrotic. This is done either percutaneously, via laparoscope, or in open surgical settings. In Ablation Mode, power delivery times can be set from 1 to 10 minutes per delivery. The efficiency at which different types of soft tissue receive MW energy differ based on the electrical properties of the tissue. The design differences in certain Certus Ablation Probes are intended to optimize the efficiency of energy transferred from the probe into different tissue types. Model Certus LK probes are designed to optimize energy transfer efficiency in liver tissue based on tissue properties.

Ablation time and power will also be controlled via the system display, which has buttons to control for Time and Power. Pressing the buttons next to the Time box adds or subtracts from the Target Time in 1-minute increments. The buttons next to the Power box add or subtract from the Power in 5-Watt increments.

Each connected probe must successfully pass a functional test before Tissu-Loc™, Ablate, or Cauterize buttons are activated. The functional test must be conducted and passed before a probe may be used for ablation or surgical functions. Once a probe passes, the functional controls become active.

Pressing the Ablation Tissu-Loc™ button starts the CO_2 cooling system to cool the Tissu-Loc™ zone in the probe to between 0 and -15°C. Once the Tissu-Loc™ Zone temperature reaches -5° C, the button turns gray, a green check mark appears on the button, and the button text reads 'Stop Tissu-Loc™.

The Probe Temperature is displayed below the probe image. A green highlighted outline appears around the Time box to indicate that power is being delivered. The Time display begins to count down from the target Time or count up to the target Time. An audible tone sounds continuously to indicate that power is being delivered. If more than one probe is delivering power, the audible tone changes pitch.

When the Stop Ablate button or Stop All Ablation Bar is pressed, energy delivery is stopped, and the Ablation Time is displayed below the Time Box. This indicates the total time that power has been delivered via that probe. The probe temperature remains on the display.

A cauterizing feature is available to cauterize the insertion track when removing the probe from the patient. This feature is to cauterize the insertion track only. It should not be used to ablate or cauterize target tissue. Only one probe can be used in Cauterize mode at a time. No other probes may be delivering energy when cauterizing with a probe.

After the probe is removed from the patient, the Certus Ablation System cart may be wheeled to the side to allow the doctor to clean and bandage the probe insertion site.

c. Warnings and precautions

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

Important: Probe temperatures are highly dependent on tissue variables such as perfusion and vasculature. Probe temperatures are likely to vary from procedure to procedure based on these tissue variables. These temperature variations do not, by themselves, indicate a malfunctioning probe or system.

Electrosurgical/electrocautery devices may interfere with the Certus system and cause system errors. Ensure that all Certus probes are removed from the patient prior to using electrosurgical/electrocautery devices.

Use only Certus Ablation Probes from NeuWave Medical with the Certus Ablation System. Probes from other manufacturers may cause patient injury or fail to function properly.

The Certus system uses a CO_2 cooling system where all other MW 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 system does not introduce new hazards or intended uses.

This product should only be used by clinicians and staff properly trained in the use of the technology and its associated warnings and cautions.

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

7.2.4. Study Procedures

Screening

Patients will be consented prior to any actual study-specific screening procedures being conducted. Patients will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process and signing the Informed Consent Form (ICF).
- Verification of the eligibility criteria (Section 7.1) by the Principal Investigator (PI) and/or authorized investigators. The verification must be conducted by the PI and/or authorized investigators prior to performing any study-related procedure or completing any form associated with this study.

Screening Failures

Screened patients who are not enrolled will be considered screen failures. For patients who are determined to be screen failures, only the following data will be recorded on the eCRF:

- Informed consent date.
- Demographic information (age, race, gender, and ethnicity).
- Reason for screening failure.

Randomization

This is a single-arm study. Hence, there will be no control or comparison group, and therefore no need for randomization.

Visit 1 – Baseline/Screening Visit

The following screening activities will occur within 14 days of the study's original ablation procedure:

- The patient must be given ample time to review and sign the ICF.
- Collect demographic information (year and month of birth, sex, race, ethnicity).
- Review and collect medical, surgical, and radiation histories, including alcohol consumption and hepatitis, if applicable. Note: HCC diagnosis does not need to be reported as medical history.
- Review inclusion/exclusion criteria and determine if the patient is eligible for participation.
- Pain, using the Numeric Pain Rating Scale (NPRS).
- Quality of Life questionnaires: EORTC QLQ-C30 and liver-specific EORTC QLQ-

HCC18.

- At minimum, an MRI of the liver must be taken at Baseline/Screening (per each study site's SOC) to ascertain tumor type, location, and size (measured in longest diameter and the diameter that is perpendicular to this longest diameter). The MRI must be taken within 14 days prior to ablation (Visit 2A). Ultrasound and/or CT are optional.
- Laboratory tests must be performed within 14 days prior to ablation (Visit 2A); otherwise the test(s) must be repeated.
    - Coagulation tests (PT, APTT, and INR).
    - Liver function tests (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, and total protein).
    - Renal function tests (Urea, creatinine, and electrolytes [sodium, potassium, and chloride]).
    - Complete blood count (differential cell count and platelet count).
    - Alpha-fetoprotein test.
    - Serum pregnancy test, for women of childbearing potential only.
- ECOG performance status.
- Child-Pugh score.
- ASA score.
- Include all relevant medications taken within 14 days prior to the ablation (Visit 2A). Relevant medications include chemotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, and those used for hepatitis (if concurrently treating).

Visit 2 – Ablation Through Discharge

The ablation procedure (Visit 2A), followed by post ablation observation and discharge (Visit 2B).

Visit 2A—Day of Ablation

Confirm inclusion and exclusion criteria prior to performing the activities below and collecting the respective data:

- Ultrasound and/or CT scan to guide the probe to the tumor and confirm accurate placement of the probe prior to emitting the microwaves. For ultrasound, a video of the ablation may be submitted to the Sponsor. The ultrasound videos will be used to review microbubble formation to see if there is a correlation with ablation area.

- Procedure details:
    - Complete procedure time.
    - Ablation time.
    - Anatomical location of ablation.
    - Number of probe placement attempts.
    - Number of ablations.
    - Ablation maximum power and time used for each probe and ablation.
    - Guidance method used.
    - Number of ultrasound and/or CT scans performed for probe and margin assessment.
- Device accountability: type(s) and number of probes used.
- Any update to relevant concomitant medications. Exclude the elements of the medications that compose the anesthesia.
- All AEs and SAEs.

Visit 2B—Post ablation

The following data must be collected post ablation (up to 7 days after an ablation procedure):

- Pain, using the NPRS.
- Quality of Life questionnaires: EORTC QLQ-C30 and liver-specific EORTC QLQ-HCC18.
- MRI scans of the liver (within 7 days after completion of ablation procedure to confirm complete tumor ablation). The MRI scans will be reviewed for reconciliation with the data provided by the treating physician regarding the ablation.
- Laboratory tests.
    - Coagulation tests (PT, APTT, and INR);
    - Liver function tests (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, and total protein).
    - Renal function tests (Urea, creatinine, and electrolytes [sodium, potassium, and chloride]).
    - Complete blood count (differential cell count and platelet count).
    - Alpha-fetoprotein (AFP) test.
- ECOG performance evaluation.

- Length of hospital stay.
- Complete tumor ablation evaluation.
- Any update to relevant concomitant medications.
- Relevant concomitant procedures.
- All AEs and SAEs.

Post Ablation Follow-up Visits 3 to 11 (End of Study)

The following data will be collected post ablation at the post ablation follow-up visits, from Visit 3 through the end of the study (Visit 11), as follows:

- Pain score, using the NPRS (Visit 3 only).
- Quality of Life questionnaires: NPRS pain score, EORTC QLQ-C30 and liver-specific EORTC QLQ-HCC18.
- MRI of the liver.
- Laboratory tests.
    - Coagulation tests (PT, APTT, and INR).
    - Liver function tests (AST, ALT, GGT, albumin, indirect, direct and total bilirubin, and total protein).
    - Renal function test (Urea, creatinine, and electrolytes [sodium, potassium, and chloride]).
    - Complete blood count (differential cell count and platelet count).
    - Alpha-fetoprotein (AFP) test.
- ECOG performance status.
- Complete tumor ablation evaluation (Visit 3 only)
- Local tumor progression (LTP) to be evaluated by a study physician based on MRI imaging. All MRI scans are to be submitted to the Sponsor.
- Progression-free survival to be evaluated by a study physician based on MRI imaging or may be reported by a patient's primary treating oncologist, if different than the study physician. If there is a progression, the study physician should specify if the progression is of the original target tumor, a new HCC tumor in the liver, or a distant metastasis.
- Any update to relevant concomitant medications.
- Relevant concomitant procedures.
- All AEs (if within 30 days post an ablation procedure).
- All SAEs through end of study.

Note: Repeat ablations may be performed on target tumor(s) only.

Unscheduled Visits

The following data will be collected at all unscheduled visits:

- Reason for the unscheduled visit.
- Relevant concomitant medications.
- Relevant concomitant procedures.
- AEs (if within 30 days post an ablation procedure) and all SAEs.

7.3. Monitoring Plan

This study will be monitored by the Sponsor to ensure:

- The rights and well-being of the patients 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 ensure 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 on-site 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.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical Design, Method and Analysis Procedure

This is a single-arm, prospective, multicenter study designed to evaluate the efficacy and safety of the NeuWave Certus Microwave Ablation System in the treatment of Chinese patients

who have a single HCC tumor up to 5 cm or who have a maximum of 3 HCC tumors of up to 3 cm per tumor.

Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum. Confidence intervals will also be provided for procedure-related variables. A detailed Statistical Analysis Plan (SAP) describing all planned analyses of data collected in this study will be finalized prior to any analysis of data.

There will be three analysis populations defined for summary of data collected in this study. The primary analysis of safety and effectiveness endpoints will be performed on the Full Analysis Set, defined as all patients who are enrolled in the study, are not part of the run-in phase, and have the NeuWave Microwave Ablation System used for ablation. A Per Protocol analysis set will be defined as all patients in the Full Analysis Set who have no major protocol deviations. Effectiveness analyses will be repeated for the Per Protocol Set. The Safety Set will include all patients who provide informed consent and have MW ablation attempted with the NeuWave system and includes run-in phase patients. The Safety Set will be used for summarization of safety endpoints only. Safety and effectiveness data collected on patients participating in the run-in phase may be summarized separately from the remaining patients. There will be at least one planned subgroup analysis based on whether or not patients have a repeat ablation in the first 30 days to correct a margin (A1 to A0). A summary of all efficacy endpoints as well as adverse event summaries will be provided for all patients who only have the initial, planned ablation procedure at Visit 2A. These summaries will also be provided for all patients who receive a repeat ablation in the first 30 days.

The number and percentage of tumors achieving Technical Success will be summarized and a 95% confidence interval will be estimated. Technical Success will be evaluated based on the margin achieved after the first ablation and prior to any repeat ablations within the first 7 days.

A similar summary will be provided for Technical Efficacy. This endpoint will be based on the scan obtained at Visit 3 and will count as successes patients with A0 or A1 margins in that scan and who did not have an A2 margin since the Visit 2B scan. Additionally, if a patient received a repeat ablation for correcting a margin (to go from A1 to A0) within the first 30 days, this will also count as a success. Patients with repeat ablations to correct an A2 margin from Visit 2B to Visit 3 will not count as success for Technical Efficacy. The number and percentage of tumors with A0 and A1 margins will be presented as a sub-categorization within each presentation of Technical Success and Technical Efficacy, as well as a summarization for the number and reasons for repeat ablations through Visit 3.

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. Any repeat ablation required after Visit 3 (Month 1) will be identified as an instance of local tumor progression. A similar summary will be provided for the 36-month overall and progression-free survival rates.

The number and percentage of patients experiencing AEs will be summarized at the preferred term level using the Society of Interventional Radiology (SIR) clinical practice guidelines for event categorization. A similar summary will also be provided for device-related AEs, procedure-related AEs, all SAEs, device-related SAEs, and procedure-related SAEs. Adverse event rates will also be estimated using cumulative patient years of exposure as the denominator as well as total number of patient ablations.

Three analyses of study data are planned. The first will occur after all enrolled patients have completed the 1-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 1-month post-operative safety profile of patients undergoing MW ablation. A similar analysis will occur after all patients have completed the 12-month visit and will include a summary of local tumor progression rates as well as safety through one year. There are no plans to use the results of either analysis for the purpose of stopping the study early. The third analysis will occur after all patients have completed study participation.

8.2. Calculation of Sample Size

8.2.1. Total Sample Size

The total sample size will be 137 patients. This includes 3 patients at each site who will be part of the run-in phase. There are no stated hypotheses in this study from which a power calculation and sample size determination will be performed; rather, a minimum of 100 patients providing data to at least 1 year is determined to be sufficient to provide an evaluation of safety and effectiveness of the NeuWave Microwave Ablation System. In anticipation of up to 20% dropout, a total of 125 patients will be enrolled after completion of the run-in phase for a total of 137 patients.

8.2.2. Minimum and Maximum Number of Patients in Each Clinical Trial Institution and Reasons for Determination

A total of 137 patients will be enrolled across the 4 study sites. There is no limitation on the number of patients each participating site may enroll. Significance Level and Power of Clinical Trial. No significance level is specified as no hypotheses are being tested in this trial, and therefore no determination of power is made.

8.3. Expected Dropout Rate

The expected dropout rate in this study is 20%.

8.4. Criterion of Acceptability/Unacceptability of Clinical Trial Result

No specific hypotheses are identified from which an acceptability criterion is determined. Evaluation of acceptable performance of the NeuWave Microwave Ablation System will be made through a comprehensive evaluation of all data collected in this trial and put in context with other available therapies for HCC.

8.5. Criteria and Reason for Terminating the Trial based on the Statistical Results

There are no planned analyses whose intent would be to stop the study early due to futility or superiority.

8.6. Statistical Method of All Data, together with the Handling Method of Missing, Unused and Error Data (including Termination and Withdrawal Halfway) and Unreasonable Data

All analyses will be performed only on patients undergoing ablation with the NeuWave Microwave Ablation System and only observed data will be analyzed. There will be no imputation of missing data for any parameters or for early terminated patients. At a given interim analysis time point, if a patient has not discontinued from the study, then the patient will be considered censored as of the date of the interim database lock for that analysis unless they have had an occurrence of the given endpoint prior to that interim database lock date. For time to event endpoints in the final analysis of data, patients who have not experienced an event will be considered censored at the last known visit date.

8.7. Reporting Procedure of Deviation from Original Statistical Plan

Any changes from the original planned statistical analyses will be specified in the protocol revisions, if applicable, and/or in a final or amended statistical analysis plan.

8.8. Selection Criteria and Reason of Patients Included in the Analysis

All patients that meet the inclusion/exclusion criteria are considered to meet the requirements for recruitment. Definitions of analysis sets are included in Section 8.1.

9. DATA MANAGEMENT

The individual patient data collected during the period of this trial will be recorded in the corresponding study database. The captured data will be reviewed by the data management team and other applicable Sponsor study team members. Any unexpected or missing data points will generate a query for the site to assess and resolve. Sponsor provided monitors will be available for questions and follow-up with the sites, as needed.

When all patients complete all follow-up evaluations and the corresponding data is entered, this study will be closed. Data analysis will be performed following database lock.

10. FEASIBILITY ANALYSIS

10.1. Likelihood Analysis of Success

The Certus Microwave Ablation System and Accessories have been cleared by the United States (US) Food and Drug Administration (FDA) and has been in clinical use since 2011 in the United States. The growing popularity of the Certus Microwave Ablation System result from

its low risks of complications and high effectiveness in ablating tumors of the liver, lung, and kidney. Pre-clinical and clinical data has shown that MW 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).[7]

The largest clinical experience using MW ablation to treat HCC comes from China, in part due to early adoption of MW ablation systems available in Asia. That multicenter study of 1007 patients with primary liver cancer showed a technical success of 97.1% (1276/1363) and a local tumor progression rate of 5.9% (78/1363) with a mean follow-up time of 17.3 months (range, 3 to 68.9 months). The 1-, 3- and 5-year overall survival rates were 91.2%, 72.5% and 59.8%, respectively.[5]

Adoption of MW ablation systems has previously been limited by technical problems associated with suboptimal power handling, large antenna diameter, antenna shaft heating and unpredictable heating patterns. Despite these limitations, the results of clinical MW ablation studies have historically compared favorably with those of RF ablation. In recent years, MW ablation systems have advanced. The Certus Microwave Ablation System is a high-powered, gas-cooled, multiple antenna-capable MW device, allowing physicians to realize the theoretical heating advantages of MW energy compared with other ablation modalities.

Microwave ablation of HCC treatment is a minimally invasive procedure that may be performed in an outpatient setting and generally takes less than 2 hours for preparation and treatment. The patient is required to return to his or her study site for 9 follow-up visits over the course of 3 years or until early discontinuation for reasons such as (but not limited to) withdrawal of consent, physician decision to withdraw the patient, lost to follow up, or death.

10.2. Likelihood Analysis of Failure

In a prospective study in China, the rate of major complications (3.8% of patients) was low and no deaths occurred within 30 days of ablation.[6] To date, more than 400 units of the Certus Microwave Ablation System and Accessories have been sold in the United States, Canada, European Union, and Singapore, where thousands of patients have been successfully treated. In recent years, MW ablation is gaining momentum in China. Because of this growing popularity of MW, failure to meet total enrolment (137 patients) in approximately 8 months, as stipulated by the protocol, is unlikely. Also, because of the low rate of major complications in patients who have been treated with MW ablation, it is unlikely that the study will be discontinued because of safety concerns.

11. DEVICE MANAGEMENT

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 sites.

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 entire 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 patient'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 to check inventory. At the end of the clinical trial all unused study devices must be returned to Johnson & Johnson Medical (Shanghai) Ltd. with the appropriate study device return form.

12. QUALITY CONTROL OF CLINICAL TRIAL

During the clinical study, the Sponsor and investigator should execute their respective responsibilities according to the Good Clinical Practice for Medical Device Trials and applicable related Chinese and international regulations. They should also strictly follow the clinical trial protocol to ensure the quality of clinical trial.

The Sponsor will ensure proper training on the clinical trial protocol and the use and maintenance of investigational medical device for all investigators participating in the trial, to ensure the consistency in the implementation of clinical trial protocol, the use of investigational medical device.

During the implementation of study, the Sponsor is responsible for monitoring each phase of the clinical trial. The clinical monitor employed by the Sponsor or appointed representative should comply with the related standard operating procedure (SOP) and clinical trial protocol that are established by the Sponsor to monitor the clinical trial, to ensure the complete, accurate, true and reliable data.

To ensure the quality of study, the Sponsor may authorize the eligible QA auditor to audit the clinical trial, as needed. The investigator should allow the auditors to review the original data and documents related to this study after receiving the notification.

When the food and drug regulatory authority, competent department of health and family planning or other regulatory agencies send the inspection personnel to carry out the inspection, the clinical trial institution and investigator should cooperate and immediately notify the Sponsor.

13. CLINICAL TRIAL ETHICAL ISSUES AND INFORMED CONSENT

13.1. Ethical Concerns

Participating investigators will ensure that this protocol, the ICF, and if applicable, any protocol amendments or other written information provided to the patients that assist in the decision to participate are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical investigation. Participating

investigators will be required to promptly report to the IRB/EC as required by the IRB/EC's policies. Additionally, investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to study patients or others.

Before the patients participate in the clinical trial, the investigator must fully explain this study and answer all questions raised by patients. Each patient (or legally authorized representative) must voluntarily sign and date the informed consent form (and other documents as per local regulations) that is approved by the Ethics Committee prior to implementing any study-related tests or procedures that are not SOC. The process of obtaining the informed consent needs to be clearly documented in the original record of the patient. The patient may request to withdraw the informed consent at any time during the study. This withdrawal will not affect the subsequent therapy of available / provided to the patient.

The production of investigational product should meet the relevant requirements of applicable quality management system for medical devices. The processing and storage of investigational product should meet the requirements of specifications and related standard operating procedure. The investigational product should be used according to the approved protocol and related operation instructions and IFU.

The collection, use, and disclosure of all personal data (including the patient health and medical information) should comply with the applicable laws and regulations regarding the personal data protection and security. 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.

13.2. Approval of Trial Protocol

The trial protocol should be internally approved and filed according to the company's SOP prior to submitting to the external agency (including but not limited to the government regulatory agencies, Ethics Committee).

The clinical trial protocol should not be implemented until the written approval is obtained from the Ethics Committee according to the relevant requirements of laws and regulations.

13.3. Process of Informed Consent and Text of Informed Consent Form

13.3.1. Process of Informed Consent

The informed consent of all potential patients must be obtained prior to performing any study tests/procedures that are not SOC. Once the investigator determines that the patients are suitable for participating in this study, the investigator must explain the background of the study presented and the benefits and risks of surgery and study to the patients and answer the questions raised by patients. Only the patient who signs the informed consent form that is approved by the EC prior to participating in the study is eligible to participate in this study.

Each patient (or legally authorized representative) must sign and date the informed consent form that is approved by the EC (and other documents as per local regulations) prior to

implementing any study-related items or operations not belonging to the standard treatment and after the nature of this study is fully clarified.

The process of obtaining the written informed consent needs to prove that the patients volunteer to participate in this study. All aspects of this study must be clarified to the patients prior to signing the informed consent form. The process of obtaining the informed consent must be clearly documented by the investigator and/or designated person in the original clinical trial documents of patients. The investigator has responsibilities to ensure the process of obtaining the informed consent is implemented according to the Good Clinical Practice for Medical Device Trials and related regulations, such as ISO 14155, the Declaration of Helsinki.

13.3.2. Text of Informed Consent Form

The ICF is available as a separate attachment.

14. REGULATIONS OF ADVERSE EVENT AND DEVICE COMPLAINT REPORTING

14.1. Adverse event

An AE is defined as any undesirable clinical occurrence in a patient. All AEs, whether attributable to the device/procedure or not, are to be recorded in the eCRF and reported to the Sponsor.

The investigator should determine whether an AE occurs and determine its relationship to the study device or surgery at each evaluation for the patients recruited for the clinical study. A change in severity may constitute a new reportable AE.

All applicable AEs, study device faults and other product problems must be recorded in the medical record and entered in the CRF. All AEs need to be recorded in the Electronic Data Capture (EDC) system (also called study database) within 2 weeks of site awareness.

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

Mild: Awareness of signs or symptoms, but does not interfere with the patient's usual activity, or is a transient event that resolves without treatment and with no sequelae.

Moderate: A sign or symptom, which interferes with the patient's usual activity.

Severe: Incapacity with inability to do work or usual activities.

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

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

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

14.2. Serious Adverse Event

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

- Resulted in death: An AE that resulted in the patient's death.
- Life-threatening illness or injury: The patient was at imminent risk of dying at the time of the AE.
- Permanent Impairment: An AE that resulted in permanent impairment of a body function or permanent damage to a body structure.
- Required in-patient or prolonged hospitalization. Note: If a patient has prolonged hospitalization due to having an additional ablative procedure to enhance the ablative margin and for no other adverse event, this should not be considered an SAE.
- Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body or body function.

- Led to fetal distress, fetal death or congenital abnormality or birth defects.
- A persistent or significant disability or incapacity.

Notes:

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

14.3. Device Complaints

A device complaint (may also be known as 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. A device complaint may or may not be associated with an AE/SAE.

Device 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

Device complaints must be reported to the Sponsor. If a Johnson & Johnson Medical (Shanghai) representative is made aware of a product complaint, the event should be reported within 24 hours of the J&J representative's awareness. The device concerned should be retained if possible. Johnson & Johnson Medical (Shanghai) representatives will organize collection of the device for evaluation.

The investigator should record all AEs and device deficiencies that occur during the clinical trial. The investigator should also work with the Sponsor to analyze the causes of the events. If needed, the written analysis report will be generated and present guidance pertaining to the continuation, discontinuation, or termination of the trial, and report to the administrative department responsible for clinical trials of medical devices. After reviewing the report, the

administrative department will forward the report to the Ethics Committee of the clinical trial institution for review.

14.4. Reporting Procedure, Contact Information

The investigator should provide the sufficient treatment for any AE of any patients, including the laboratory detection value with clinical significance whether or not it is related to this study.

From ablation of the patient, all AEs related to the patient's participation in this study should be followed up until the event is resolved, or if the event causes the permanent damage, it should be followed up until the event is stable and the clinical outcome is determined.

All AEs and SAEs will be reported for 30 days after any ablation procedure (original or additional); after 30 days post an ablation procedure through the end of the study, only SAEs will be reported. All AEs should be followed up, until the AE is resolved, stable or the study is completed.

The investigator should record the nature, severity, treatment and outcome of the AE or SAE, and determine whether it is related to the study device, or the ablation procedure specified in the study protocol. The investigator will report all AEs to the Sponsor via the study database EDC.

The investigator must submit any SAEs that occurred in the study and the device deficiencies that may cause an SAE, to the Sponsor and National Medical Products Administration (NMPA) (or designated person) immediately after being informed of the event. If required by the Sponsor, the further information should be provided.

All SAEs need to be followed up until the event is resolved (with or without sequela). When the event is not resolved or stable at the end of study, the medical monitor in this clinical study will decide whether it is necessary to collect the further follow-up information.

The investigator and Sponsor should report the SAEs which occurred in the study, and the device deficiencies that may cause an SAE, to the regulatory authorities at every level according to the requirements of laws and regulations.

For all SAEs and device deficiencies that may cause SAEs, the Sponsor should report to the Food and Drug Administration where the clinical study was filed and the competent department of health and Family Planning Commission within 5 work days after awareness. The Sponsor should also inform other clinical trial institutions/sites and investigators that participate in the trial and inform the Ethics Committees by their medical device clinical trial management departments in a timely manner.

The study device with a device complaint should be returned to the Sponsor according to the instructions given in Section 11 of this study protocol. Once a device complaint is found, the site should inform the Sponsor as soon as possible, and report the device related information on the relevant CRF.

Refer to Section 14.3 for details of the device complaint report process. The contacts to report SAEs and device complaints are as follows:

Adverse events

China AE reporting: Neuwave_China_AE_Reporting@its.jnj.com

Global AE reporting: ETHMedAlerts@its.jnj.com

Medical device complaints

Local CHU reporting: ChinaCustomerQuality-CS@its.jnj.com

Global CHU reporting: Productcomplaint1@its.jnj.com

15. DEVIATION FROM CLINICAL TRIAL PROTOCOL AND REGULATIONS FOR CLINICAL TRIAL PROTOCOL AMENDMENT

The study protocol deviations are defined as the circumstances that fail to comply with the requirements of clinical trial protocol intentionally or unintentionally.

All protocol deviations should be reported as protocol deviations to the Sponsor via the study EDC database. The reporting should include the date and reason for protocol deviations. The investigator should also report the protocol deviations to the EC and all related department according to each site's requirements and in combination with the requirements and procedures of the EC.

If a protocol amendment occurs, the Sponsor or designated person should submit a summary of changes of the study protocol to the investigator, regulatory authority, and the Ethics Committee, etc. according to the relevant laws and regulations. All major amendments must be approved by the Ethics Committee and regulatory authority (if needed) prior to implementing any changes to study procedures.

If an amendment likely has major impact on the following items, this amendment belongs to the major amendment:

- Safety or physical or mental health of patients;
- Scientific value of trial;
- Implementation or management of trial;
- Quality or safety of investigational medical device specified in the trial.

16. DIRECT ACCESS TO SOURCE DATA AND DOCUMENT

The source data is defined as all information in the original record and its approved copy regarding the clinical findings, observations and other activities in the clinical trial, which can be used for reproduction and evaluation of clinical trial. The source documents are documents on which the source data is recorded, including printed, paper or electronic documents.

The patient's medical record and other study related documents (source documents) must be maintained and retained by the investigator. The investigator should allow the monitors and auditors/inspectors to review all relevant patient records, including but not limited to the following information:

- Medical/physical condition of the study patient that meets the inclusion criteria prior to participating this study;
- Process of informed consent;
- Operational description of use and implantation of the study product;

- All inspection results and follow-up;
- Examined printed output file or report (for example, X-ray film) that is dated and signed;
- Description of AE and follow-up of AE (description of event, severity, date of occurrence, duration, correlation with the study device, study procedure, outcome, and treatment of the AE, concomitant medications when the AE occurs);
- Description of device complaint;
- Study patient's status at the end of the study or withdrawn from the study.

Appropriate source documents must be available for reviewing during the monitoring visit. The Sponsor expects that the study coordinator and/or investigator will also be available for questions during monitoring visits.

Those patients that specifically consent to the additional research analysis will have relevant patient characteristics, treatment and outcome data, that is already being captured for this study, compiled with the same type of data from consenting patients from other NeuWave Medical studies used in a separate analysis. These data will be collectively used for Time and Power predictive analytics and reported in an aggregate fashion. Patient/patient identifiable information will not be used except for the patient's study number. The goal of this analysis is to characterize the optimal MW ablation parameters for specific tumor types, locations, and liver conditions.

17. FINANCES AND INSURANCE

See the relevant study contract and insurance document.

18. CONFIDENTIALITY

The personal data of the patient participating in the trial is confidential; however, the Ethics Committee, NMPA, competent department of health and family planning, or the Sponsor and its authorized representative may review the personal data of the patient participating in the trial for the purpose of their work according to the local established procedure.

The personal data of the patient should be kept confidential during the entire period of clinical trial, and it should be ensured that the source data can be verified through the supporting information. A unique patient ID number (site number and patient number) will be used to identify all data for every enrolled patient. So long as the data is kept strictly confidential and that the privacy of the patient is ensured to be protected, the data related to this study may be available to third parties (for example, under the audit of regulatory authority).

19. AGREEMENT ON THE PUBLICATION OF TRIAL RESULTS

Following completion of this study, an article might be prepared and published in a scientific journal. No major results or experience from any individual site in this study can be published before the multicenter trial results are prepared and published. An exception to this rule will need prior approval from the Sponsor. A second publication may be generated by corresponding principal authors. The final analysis and review from all trial data are required to be reviewed and approved by the Sponsor.

20. RESPONSIBILITIES THAT EACH PARTY SHOULD BEAR

20.1. Responsibilities of the Sponsor

1) The Sponsor is responsible for the initiation, application, organization and monitoring of clinical trial.

2) The Sponsor is responsible for the organization to establish and modify the investigator's brochure, clinical trial protocol, informed consent form, Case Report Form, relevant standard operating procedure and other relevant documents, carry out the training required for the clinical trial, and provide these documents to the investigators before the study starts.

3) The Sponsor should select the qualified trial institution and investigators.

4) The Sponsor should sign a written agreement with the clinical trial institution and the investigator regarding the clinical trial.

5) The Sponsor should provide qualified study product according to the regulatory requirements. The Sponsor should be responsible for the safety of investigational medical device in the clinical trial. The AE, SAE, and the device complaint that may cause an SAE should be collected and reported in accordance with the provisions.

6) The Sponsor should inform the regulatory authority at every level when the Sponsor decides to suspend or terminate the clinical trial or at the end of the study.

7) The Sponsor should ensure the investigator conducts the study strictly in compliance with the clinical trial protocol, corrects the protocol deviations in a timely way, and reserves the rights to report, to the regulatory authority, any of issues related to this.

8) The Sponsor should bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of patients, except for damages due to the fault of medical institution and medical staff in the diagnosis and treatment.

9) The Sponsor should select qualified monitors for monitoring and organizing any inspections, as appropriate.

20.2. Responsibilities of Clinical Trial Institution and Investigator

1) The clinical trial institution should evaluate the relevant resources according to the features of investigational medical device prior to the clinical trial, to decide whether to participate in this clinical trial.

2) The clinical trial institution should properly keep the records and documents of clinical trial according to the agreement with the Sponsor.

3) Make sure that the investigators responsible for the clinical trial have the qualification in accordance with the requirements of related laws and regulations.

4) The administrative department for clinical trial of medical device of clinical trial institution should cooperate with the Sponsor to apply to the Ethics Committee and submit the relevant documents prior to the clinical trial according to requirements.

5) The investigator should ensure that the relevant workers participating in the trial have the enough resources and proper training and keep the training related documents.

6) The investigator should ensure to use the investigational medical device only for the patients of this clinical trial.

7) The investigator may not charge patients any fees for participating in the study.

8) The investigator should strictly follow the clinical trial protocol, with the exception of emergency circumstances when the patient faces the direct risk and needs immediate clinical measures, which can be reported later in a written form.

9) The investigator is responsible for recruiting the patients, communicating with the patient or its legal representative before signing the informed consent.

10) The investigator should protect the rights, safety and health of the patients.

11) In case of an AE occurring in the clinical trial, the investigator should protect the safety of the patients and timely report the event to the regulatory authority.

12) The investigator should record all AEs occurring and device deficiencies found in the process of clinical trial, work with the Sponsor to analyze the causes of the events, generate the written analysis report, present the comments on the continuation, discontinuation or termination of the trial, and report to the Ethics Committee by the administrative department for clinical trial of medical device of clinical trial institution for review.

13) The investigator should make sure that the clinical trial data is accurately, completely, clearly and timely recorded in the Case Report Form.

14) The clinical trial institution and investigator should make sure that the data, documents and records generated in the clinical trial are timely, true, accurate, clear, and attributable.

15) The clinical trial institution and investigator should accept and cooperate with the

monitoring and audit of the Sponsor, the supervision of the Ethics Committee, and the inspection of the Food and Drug Administration, competent department of health and family planning, etc., and provide all required records related to the trial.

16) If the clinical trial needs to be suspended or terminated, the patients should be informed accordingly. It should be ensured that the patients receive the proper care and follow-up. The clinical trial institution and investigator should also report this in accordance with the regulations and provide a detailed written explanation. The relevant report should be submitted to the local Food and Drug Administration at the provincial, autonomous regional and municipal level, if necessary.

17) The clinical trial institution and investigator reserve the rights to report to the regulatory authority at every level when the Sponsor violates relevant laws and regulations.

18) The investigator should complete all records and reports at the end of clinical trial. The investigator should also ensure that the received investigational medical devices are properly handled and recorded according to the requirements.

20.3. Responsibilities of other interested parties

See the study related contract, which is available as a separate attachment.

STATEMENT OF INVESTIGATOR

I agree to:

1. Conduct this clinical trial in strict accordance with the requirements of the Declaration of Helsinki, China's current laws and regulations and trial protocol.
2. Record all required data correctly in the study EDC database and input, review, and approve the clinical trial report on schedule.
3. Use the investigational medical device only for this clinical trial, accurately and completely record the investigational medical device receipt and use condition during the clinical trial and keep these records for review.
4. Allow the monitor and inspectors authorized and dispatched by the Sponsor and regulatory authority to monitor, inspect and audit this clinical trial.
5. Strictly implement the terms in the clinical trial contract/protocol signed by all parties.

I have read thoroughly the clinical trial protocol, including the above statements, and I agree to all the above contents.

Comments of Sponsor Signature (Stamp) Date: DD/MM/YYYY

Comments of investigator Signature Date: DD/MM/YYYY

Comments of clinical trial institution of medical device Signature (Stamp) Date: DD/MM/YYYY

APPENDIX 1: STUDY DEVICES CODE LIST

Model	Description
NWC2CN1N	NeuWave Certus™ Microwave Ablation System
CTBKT1	CT Bed Rail PDM Mounting Bracket, Standard (GE, Philips)
CTBKT2	CT Bed Rail PDM Mounting Bracket, D68 X W585 Standard (Siemens)
CTBKT3	CT Bed Rail PDM Mounting Bracket, D48 X W656 Standard (Toshiba)
CTBKT4	CT Bed Rail PDM Mounting Bracket, D88 X W645 (Siemens Alt)
CTBKT5	CT Bed Rail Mount, Flat
PDM1TBL	Table PDM Mount
PD2MSURG	CT Bed Rail PDM Mounting Bracket, 18: Long (Surgical Mount)
LK15CN	NEUWAVE CERTUS LK Probe 15CM 17ga
LK20CN	NEUWAVE CERTUS LK Probe 20CM 17ga
LK15XTCN	NEUWAVE CERTUS LK XT Probe 15CM 15ga
LK20XTCN	NEUWAVE CERTUS LK XT Probe 20CM 15ga
PR15CN	NEUWAVE CERTUS PR Probe 15CM 17ga
PR20CN	NEUWAVE CERTUS PR Probe 20CM 17ga
PR15XTCN	NEUWAVE CERTUS PR XT Probe 15CM 15ga
PR20XTCN	NEUWAVE CERTUS PR XT Probe 20CM 15ga
NWSR25CN	NEUWAVE CERTUS SR Probe 25CM 13ga

Note: These are collectively described as “study devices.”

APPENDIX 2: REFERENCES

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