Statistical Analysis Plan

A Multicenter Study to Evaluate NEUWAVE Microwave Ablation System Using Ablation Confirmation in Patients with A Soft-Tissue Liver Lesion

Protocol Number: NEU_2017_03

Protocol Version: Amendment 3 (Version 4.0), 26Jul2021

SAP Version: 1.0
SAP Version Date: 28Nov2022

A Multicenter Study to Evaluate NEUWAVE Microwave Ablation Using Ablation Confirmation in Patients with A Soft-Tissue Liver Lesion

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

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Revision History

Version Number	Version Date	Reasons for Revision
0.1	17Sep2022	First draft
0.2	13Oct2022	Incorporated team's review
0.3	25Oct2022	Incorporated team's review
1.0	28Nov2022	Final

Table of Contents

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Protocol NEU_2017_03. This SAP describes, in detail, the statistical methodology and statistical analyses for the above-mentioned protocol.

1 Study Overview

1.1 Study Objectives

The primary objective of the study was to examine whether the feedback from the AC software impacts the performing physician's (i.e., the individual performing the ablation procedure) decision making in terms of probe(s) position, ablation time, or number of ablations based on insufficient ablation margins based on the following assessments:

a. Percentage of repositions informed by AC due to sub-optimal probe placement.
b. Percentage of re-ablations informed by AC due to insufficient ablation margins.

The secondary objectives were the following:

1. Technical success - defined as ablation of the target lesion(s) according to the protocol and covered completely with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an adequate ablative margin). Technical success will be assessed by the performing physician using AC as a tool immediately following the procedure.
2. Technique efficacy - defined as ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by imaging at Visit 3.
3. Hospital resource utilization based on:
   a) Length of post-ablation hospital stay.
   b) Time to perform procedure, which includes 3 measures of time:
      - Overall procedure duration, defined as the time elapsed between loading CT dataset into the AC system and completion of MWA with last probe removal.
      - AC imaging duration, defined as the time elapsed between loading CT dataset into AC to plan for the target ablation and last use of AC to plan for the final ablation.
      - Ablation duration, defined as the time elapsed between ablation first probe puncture and removal of the last probe at the completion of the ablation.
4. Device and procedure safety through the monitoring of adverse events. Patients will be evaluated for all device-related and procedure-related AEs and all SAEs from the time of the first probe puncture (Visit 2) through study completion (Visit 3).
5. Device User Experience questionnaire will be completed by the performing physician. The first half will be completed following each ablation procedure and the second half will be completed approximately every 5 ablations (per treating physician).

6. Patient Quality of Life (QOL) questionnaires as measured by EORTC QLQ-C30 and the liver-specific QLQ-HCC18, at Visit 2 (Pre-Ablation) and at Visit 3 (6 weeks post-ablation).
7. Patient Numeric Pain Rating Scale (NPRS) questionnaire at Visit 2 (Pre- and Post-Ablation) and at Visit 3 (6 weeks post-ablation).

1.2 Study Design

This was a prospective, single-arm, multicenter clinical study that generated clinical data using NEUWAVE Microwave Ablation System with Ablation Confirmation Software in patients undergoing MWA of at least one soft-tissue liver lesion as part of the study site's SOC treatment.

2 Treatment Assignment

This was a single-arm study where all enrolled patients were ablated using the NEUWAVE Microwave Ablation System and the AC software tool.

3 Randomization and Blinding Procedures

This is a single-arm, open-label study. No randomization occurred and no blinding procedures were required.

4 Interval Windows

Interval windows are not defined for the purpose of analysis in this study outside of the visit windows that are provided in the Schedule of Assessments in Table 1 of the final protocol. There will be no assigning of observations to time points outside of the visit to which they are recorded in the electronic Case Report Forms (eCRFs). Data collected in Unscheduled Visit forms will be listed as such.

5 Level of Significance

No hypotheses are specified for this study and no p-values are being calculated. Therefore, no level of significance is specified. For selected endpoints 95% confidence intervals will be estimated.

6 Analysis Sets

The study protocol identified two analysis sets:

- The Full Analysis Set (FAS) will consist of all eligible patients who are enrolled in the study and had the ablation procedure attempted with the AC tool. Lesions from patients in FAS that had the ablation procedure attempted with the AC tool will be included on the FAS. The FAS will be the primary analysis set for safety and effectiveness endpoints. Patients followed by lesions for whom the response was "Yes" to the question "Was

ablation confirmation software used to validate probe placement?" on the Ablation Confirmation form on the eCRF will be included on the FAS.

- The Per Protocol Analysis Set (PPS) will consist of all patients who are enrolled in the study and had the AC tool utilized as part of the ablation procedure with no major protocol deviations that indicate an exclusion from PPS. Lesions from patients in PPS that had the ablation procedure attempted with the AC tool will be included on the PPS. Effectiveness analyses is planned to be repeated for the PP Set. Patients followed by lesions for whom the response was "Yes" to the question "Was ablation confirmation software used to validate probe placement?" on the Ablation Confirmation form on the eCRF and had no major protocol deviations that indicate an exclusion from PPS as per the Protocol Deviation Classification document will be included on the PPS.

7 Sample Size Justification

Given that this was an initial experience with the AC system in a general use population, a sample size of a minimum of 100 patients was deemed sufficient for estimating the repositioning rate for appropriate sizing of a subsequent study. With an expected repositioning rate of 15%, a sample size of 100 patients would control the half-width of a 95% confidence interval to less than 7%. However, the study was terminated early with a smaller number of patients enrolled than planned. The reasons for early termination are difficulty in enrolling patients to the study and other studies are gathering similar data as the current study to help inform the objectives of the current study.

8 Data Safety Monitoring Board

This study did not use a DSMB.

9 Analyses to be Conducted

9.1 General Conventions

Patient data will be summarized using listings and tables. All eCRF data will be listed per patient for all patients. Descriptive statistical analyses will be provided for pre-specified study endpoints. Summaries for continuous variables will include number of observations (n), mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include number and percentage.

Analyses will be conducted using SAS software version 9.4 or higher. During the course of analysis programming of tables that are mocked up in this SAP, minor modifications may become necessary. Examples of these minor modifications include, but are not limited to, re-wording of a footnote, addition of a footnote, re-labeling of a column, or addition or removal of a column from a listing. In cases where modifications to tables or listings are not related to a change in statistical analysis methodology or conclusions that could be made on the originally proposed methodology, then no amendment of the SAP is necessary. Any final analyses that

differ from what has been specified in this document will be identified within the final statistical output and documented within the clinical study report.

9.2 Disposition of Study Patients

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

9.3 Demographic and Baseline Characteristics

Summary statistics will be provided for patient demographic, vital sign, and pre-operative characteristics. Demographic variables include age, sex, childbearing potential for female patients, ethnicity, and race. Vital sign and pre-operative characteristics include BMI, smoking status, ASA score, CEA test and CEA value, and diagnosis of hepatitis and type of hepatitis will be summarized as the pre-operative characteristics. Demographic and baseline characteristics will be listed.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Medical history, surgical history, and treatment history will be listed.

9.4 Primary and Secondary Endpoints Analyses

9.4.1 Primary Endpoints Analyses

a. <u>At the lesion level:</u> The number of lesions that had repositioned of probe placement informed by AC software due to sub-optimal probe placement will be summarized by percentage and an exact 95% confidence interval of the percentage based on Clopper-Pearson method. Analysis will be conducted using FAS and PP analysis sets. The number of repositions informed by AC software is derived from the "Ablation Confirmation" form on the eCRF. A reposition informed by AC software is determined by an affirmative response to the question "Actions were taken due to AC software indicating probe placement was not satisfactory" and followed by choosing at least one of the three action items that are listed on the form and these lesions represent the numerator for calculating the percentage. The denominator comprises with lesions for which the following option was chosen "No actions taken despite AC software indicating probe placement was not satisfactory" along with lesions that are presented on the numerator. Lesions belong to the group "No actions taken due to AC software indicating satisfactory probe placement" are not included to the numerator or denominator.

<u>At the patient level</u>: The numerator is "Number of patients for whom AC suggested suboptimal probe placement for ***at least one lesion*** and surgeon took action." The denominator is "Number of patients for whom AC suggested suboptimal probe placement for ***at least one lesion*** and surgeon took action + Number of patients for whom AC suggested suboptimal probe placement for ***at least one lesion*** and surgeon did not take action." Patients who had all lesions belong to the group "No actions taken due to AC software indicating satisfactory probe placement" are not included to the numerator or denominator. An exact 95% confidence interval of the percentage will be estimated.

b. At the lesion level: The number of lesions that had re-ablations informed by AC software due to insufficient ablation margins will be summarized by percentage and an exact 95% confidence interval of the percentage. Analysis will be conducted using FAS and PP analysis sets. The number of re-ablations informed by AC software is derived from the "Ablation Confirmation" form on the eCRF. A re-ablation informed by AC software is determined by an affirmative response to the question "Actions taken due to AC software indicating ablation margin was not complete" and followed by choosing at least one of the five action items that are listed on the form and these lesions represent the numerator for calculating the percentage. The denominator comprises with lesions for which the following option was chosen "No actions taken despite AC software indicating ablation margin was not complete" along with those presented on the numerator. Lesions belong to the group "No actions taken due to AC software indicating satisfactory margins" are not included to the numerator or denominator.

At the patient level: The numerator is "Number of patients for whom AC indicated that ablation margin was not complete for ***at least one lesion*** and surgeon took action." The denominator is "Number of patients for whom AC indicated that ablation margin was not complete for ***at least one lesion*** and surgeon took action + Number of patients for whom no actions taken despite AC software indicating ablation margin was not complete for ***at least one lesion***." Patients who had all lesions belong to the group "No actions taken due to AC software indicating satisfactory margins" are not included to the numerator or denominator. An exact 95% confidence interval of the percentage will be estimated.

9.4.2 Secondary Endpoints Analyses

1. Technical success: The number and percentage of lesions achieving technical success will be summarized and an exact 95% confidence interval will be provided. Analysis will be conducted using FAS and PP analysis sets. Technical success is captured on the "Ablation Outcome" form on eCRF. Technical success is achieved when the treating physician choose the response as "complete ablation" for the question "Per treating physician, what was the outcome of the ablation?". The summary statistics will also be presented for per patient. The technical success is considered achieved at a patient-level when all treated lesions for a patient were successful.

2. Technique efficacy: The number and percentage of lesions achieving technique efficacy will be summarized and an exact 95% confidence interval will be provided. Analysis will be conducted using FAS and PP analysis sets. Technique efficacy is captured on the eCRF based on the response as "yes" from the physician performing ablation for the question "Was technique efficacy achieved for target lesion?" from the "Technique Efficacy" form. The summary statistics will also be presented for per patient. The technique efficacy is considered achieved at patient-level when all treated lesions for a patient were successful.

3. Hospital resources utilization: Summary of endpoints related to hospital resources utilization will include number of patients (N), mean, standard deviation, median, minimum, and maximum and will be based on FAS. Following endpoints will be presented on the summary tables:

a) Length of post-ablation hospital stay. Length of post-ablation hospital stay will be derived from the Discharge and Ablation forms on eCRF. It will be derived as

Length of post-ablation hospital stay = (date and time of hospital discharge – date and time of ablation ended).

b) Time to perform procedure, which includes 3 measures of time:

i) Overall procedure duration, defined as the time elapsed between loading CT dataset into the AC system and completion of MWA with last probe removal. The overall procedure duration is captured on the Ablation Procedure form on eCRF.

ii) AC imaging duration, defined as the time elapsed between loading CT dataset into AC to plan for the target ablation and last use of AC to plan for the final ablation. AC imaging duration is captured on the Ablation Procedure form on eCRF.

iii) Ablation duration, defined as the time elapsed between ablation first probe puncture and removal of the last probe at the completion of the ablation. Ablation duration is captured on the Ablations form on eCRF under the variable name "Duration."

Other endpoints associated with hospital resources utilization will be listed.

4. Device-related and procedure-related AEs and all SAEs from the time of the first probe puncture (Visit 2) through study completion (Visit 3 or early termination from the study) will be summarized based on FAS. Further details on safety analysis are presented on Section 9.5.

5. Device User Experience questionnaire: It is measured by the "Ablation Confirmation User Evaluation Questionnaire" and completed by the performing physician. The first half will be completed following each ablation procedure and the second half will be completed approximately every 5 ablations (per treating physician). The questionnaire will be summarized by its items for the frequencies and corresponding percentages based on the FAS. A listing will be provided for the Ablation Confirmation User Evaluation Questionnaire.

6. Patient Quality of Life questionnaires: Quality of Life will be measured using EORTC QLQ-C30 and liver specific QLQ-HCC18 at Visit 2 (pre-ablation) and Visit 3.

C30 and HCC18 overall scores will be derived to have an overall representation of all domains/items in QLQ-C30 and QLQ-HCC18, respectively. The scores for C30 and HCC18 will be derived as per the guidance on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 scoring manual version 3.0.

The overall scores for each scale and the changes from Visit 2 to Visit 3 will be summarized using N, mean, standard deviation, minimum, maximum, and median based on the FAS. The overall scores for each scale will be listed.

EORTC QLQ-C30:

The EORTC QLQ-C30 (version 3.0) comprises 30 questions and provides a multi-dimensional assessment of QoL.

The QLQ-C30 is composed of both multi-item scales and single-item measures. EORTC QLQ-C30 can be combined to produce 5 functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, diarrhea) and a global measure of health status.

Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

There are four responses for each question from Q1 to Q28: from not at all, a little, quite a bit, to very much, each will be scored from 1 (not at all) to 4 (very much). For Q29 and Q30, scores will be from 1 (very poor) to 7 (Excellent).

No response (NR) means no response to any of the questions and will be considered as missing as well as not included in the analysis.

Table 1: Scoring the EORTC QLQ-C30 version 3.0

Scale	Number of items	Item range*	Item numbers
Global health status /			
Global health status/QoL	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales / items			
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnoea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhoea	1	3	17
Financial difficulties	1	3	28

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

The scoring procedures is as follows:

For each of the 15 scales/items in Table 5, a score is computed by taking the following steps:

For scales with more than one item, raw scores (RS) are the sum of scores for each item divided by number of items:

RS = (Q1 + …+Qn) / n, where n represents the number of non-missing item scores

If at least half of the component items from the scale have been answered, the raw score will be calculated as the average of the non-missing items, otherwise the raw score will be set to missing. This is equivalent to the raw score being taken as the mean of the non-missing item values.

For single item scales, the raw score is simply the score for that item. If a single-item score is missing, the single-item scale raw score is missing.

Scale scores (S) are calculated by a linear transformation to 0-100:

For Functional scales:

$$Score = S = \left(1 - \frac{RS-1}{Range}\right) \times 100$$

For Symptom scales / itemsand Global health status / QoL:

$$Score = S = \left(\frac{RS-1}{Range}\right) \times 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The EORTC QLQ-C30 has been designed so that all items in any scale have the same range. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6.

All the scales and single-item measures are linearly transformed so that each score ranges from 0 to 100. Higher scores for the global health status/ QoL scale and functioning scales indicate a higher/healthier level of functioning and a higher/better QoL respectively, whereas higher scores in symptom scales represent a higher level of symptoms/problems.

Example:

Emotional functioning (EF):
Raw score (RS) = (Q21+ Q22+ Q23+ Q24)/4
*EF score = {1 – ((RS – 1)/3)} *100*

The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Difficulties scale are not included). Prior to calculating the mean, the symptom scale/individual item scale scores need to be reversed (i.e., 100 minus the scale score) to obtain a uniform direction of all scales. The summary score will only be calculated if all the required 13 scale scores are available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed).

EORTC QLQ-HCC18:

EORTC QLQ-HCC18 includes 18 multi-item scales. These items are grouped into 6 domains (fatigue, body image, jaundice, nutrition, pain and fever). Two remaining single items address abdominal swelling and sex life. All scales will be grouped and converted to scores of 0 to 100 according to the scoring manual; a higher score represents a more severe symptom or problem.

Table 2: Scoring the EORTC QLQ-HCC18

Scale	Number of items	Item range*	Item numbers
Symptom scales / items			
Fatigue	3	3	15, 16, 17
Body Image	2	3	3, 5
Jaundice	2	3	6, 7
Nutrition	5	3	1, 2, 12, 13, 14
Pain	2	3	8, 9
Fever	2	3	10, 11
Abdominal Swelling	1	3	4
Sex life	1	3	18

** Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

The scoring procedures as below:

For each of these domains, a symptom score is computed by taking the following steps:
(1) sum across the item responses on that domain,
(2) divide by the number of non-missing items to obtain the mean of item response (RS),
(3) subtract 1 from the mean of the item responses (i.e., item response means – 1),
(4) divide by the number in Item Range
(5) multiply by 100.

This results in symptom scores that range from 0 to 100 with higher scores indicating greater symptom severity. These symptom scores can be computed if at least 50% of the items have responses (i.e., 1 item response needed for 1 item domains, 1 item response needed for 2 item domains, 2 item responses needed for 3 item domains).

HCC18 index-score is defined as the sum of all 8 QLQ-HCC18 symptom/problem scales divided by 8 (the total number of QLQ-HCC18 scales). A higher HCC18 index-score reflects a worse overall Health-related quality-of-life (HRQOL).

7. Pain scores collected through the Patient Numeric Pain rating Scale (NPRS) questionnaire at Visit 2 (pre- and post-ablation) and Visit 3 will be summarized as a continuous variable. The changes in pain score from Visit 2 (pre-ablation) to Visit 2 (post-ablation) (Visit 2 Pre-ablation – Visit 2 Post-ablation) and from Visit 2 (pre-ablation) to Visit 3 (Visit 2 Pre-ablation – Visit 3) will also be presented.

9.5 Safety Analyses

Safety will be assessed through the incidence of AEs and SAEs, which will be coded using MedDRA. The number and percentages of patients reporting AEs and SAEs will be summarized at the MedDRA system organ class and preferred term level. As a secondary endpoint of the study summaries will be provided for AEs and SAEs related to the study device, as well as for AEs and SAEs related to the study procedure. Related events are those where the relationship is indicated as Possible, Probable, or Causal relationship. Summaries of all AEs and SAEs reported within the first 30 days after the initial ablation procedure will be generated. All reported adverse events will be listed. Listings will also be provided for concomitant procedures and concomitant medications.

Safety endpoints are as follows:

- All AEs
- Serious AEs
- All AEs related to the study device
- Serious AEs related to the study device
- All AEs related to the study procedure
- Serious AEs related to the study procedure

9.6 Additional Endpoints Analyses

Counts and percentages will be provided for patient performance status as measured by the Eastern Cooperative Oncology Group (ECOG) classification at each visit. Changes in ECOG will be summarized using shift tables. A listing will be provided for ECOG performance status.

Summary statistics will be provided for the hematology parameters and chemistry parameters at each visit. Summary statistics of changes in hematology and chemistry parameters from visit 1 to visit 2, visit 1 to visit 3, and visit 2 to visit 3 will be presented.

Liver tissue assessment including severity of steatosis and cirrhosis, presence of lesion microsatellite instability, phenotype, presence of microvascular invasion, BCLC staging system, and Child-Pugh score will be summarized with number and percentages in each category.

Target lesion assessments including lesion type, shape, segments, depth, maximum dimension by X-, Y-, and Z-axis will be summarized with statistics appropriate for categorical or continuous variables. A listing for target lesion will be produced that will include subject ID, visit, lesion number, type of lesion, shape of lesion, segment number, imaging modality used for lesion measurements, liver lesion dimension, and evidence of target lesion recurrence. The listing will be presented by sorting the patient followed by visit, lesion number and segment.

Ablation procedure details that include type of anesthesia, imaging modalities used for guidance/probe placement and margin assessment, number of CT images performed for probe placement and margin assessment, liver stiffness near ablation site, amount of contrast used, duration of procedure, and total radiation exposure from the CT scanner will be summarized with statistics appropriate for categorical or continuous variables.

Ablation including lesion type, lesion number, probe used, segments, duration, max power observed, max temperature observed, and repositioning will be summarized with statistics appropriate for categorical or continuous variables.

Listing for ablation procedure will include subject ID, Number of CT scan(s) performed for probe placement, Duration of the ablation procedure, Total duration of ablation, Were there any repositions in probes during ablation and how many, reason of probe reposition, Number of CT scan(s) performed for margin assessment, Duration of the AC imaging, and Overall procedure duration.

Listing for ablation will include subject ID, lesion type, lesion number, probe, probe type, segment, Max power observed, Max temperature observed, dynamically change power during this ablation cycle for a specific probe, type of power change, and assessment of margins using CT & ablation confirmation software after ablation. The listing will be presented by sorting the patient and by lesion number.

Listing for ablation outcome will include subject ID, lesion type, lesion number, outcome of the ablation, reason for incomplete ablation, and smallest margin distance in the ablation zone.

Listing for ablation confirmation will include subject ID, lesion type, lesion number, use of ablation confirmation software to validate probe placement, actions in probe placement, type of actions taken in probe placement, reason for taking no actions, use of NeuWave ablation confirmation software to validate margin assessment, % of contraction used, actions taken regarding margin, type of actions taken regarding margin, and reasons for No actions taken despite AC software indicating ablation margin was not complete.

9.7 Plans for Interim Analysis

There are no planned interim analyses.

9.8 Handling of Missing Data

All analyses will be performed only on patients who had the ablation procedure with the AC software tool attempted and only observed data will be analyzed. There will be no imputation of missing data for any parameters or for early terminated patients.

9.9 Multicenter studies

No adjustment for center is planned in the statistical analyses.

9.10 Subgroup analyses

Subgroup analyses will be conducted for primary endpoints, selected secondary endpoints that include technical success, technique efficacy, hospital resource utilization, and adverse events, and recurrence of target lesion. The subgroups are lesion type, lesion shape, occurrence of AE, liver segment, and number of probes used. Summary statistics will be presented for each of the endpoints by subgroups. No inferential statistics will be presented. Subgroup analysis will be conducted based on FAS.

Signature Page for VTMF-18198095, V-TMF Version: 1.0

NEU_2017_03---Statistical Analysis Plan-28 Nov 2022

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To verify that the content is accurate and true to the best of my knowledge.