

Statistical Analysis Plan (SAP)

A Multicenter Observational Registry to Develop Ablation Parameter Guidance for Microwave Liver Ablation of Soft Tissue Lesions

Protocol Number: NEU_2017_04

**Protocol Version: Amendment 3 (version 4.0), 21 July
2021**

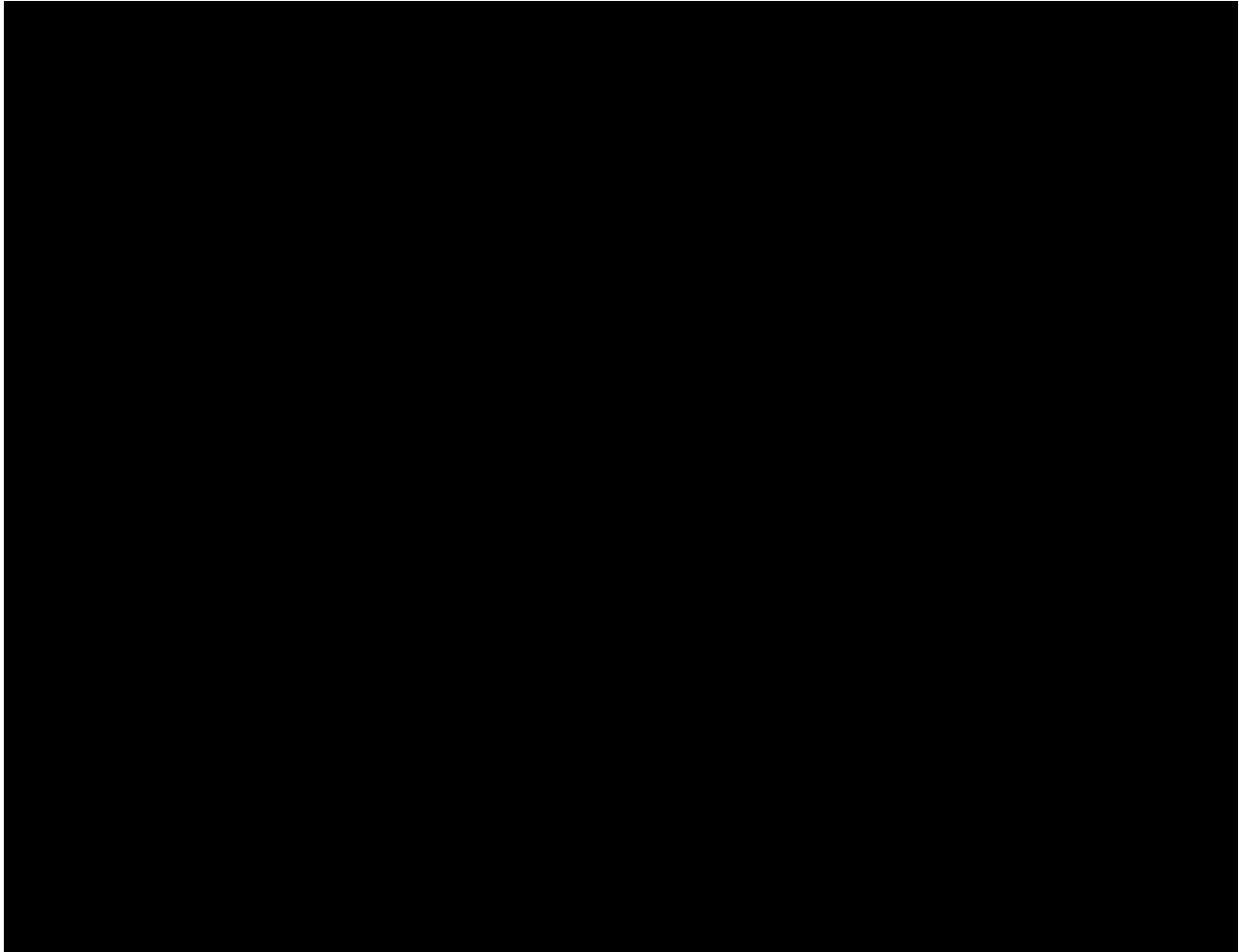
This document is a confidential communication. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written approval. This document may be disclosed to the appropriate ethics committees or to duly authorized representatives of the U.S. Food and Drug Administration or other responsible regulatory authorities, under the condition that they are requested to keep it confidential.

SAP Revision: 2.0
SAP Revision Date: 30OCT2025

**A Multicenter Observational Registry to Develop Ablation Parameter Guidance for
Microwave Liver Ablation of Soft Tissue Lesions**

Protocol Version: Amendment 3 (version 4.0), 21 July 2021

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content. Signatures are collected digitally and can be found on the last page of this document.



Revision History

Revision Number	Revision Date (DDMMYYYY)	Reasons for Revision
1.0	10Aug2023	Not applicable
2.0	30OCT2025	Details are added for analyses of primary and secondary endpoints, subgroups, and regression models.

Contents

1	Introduction	6
	1.1 Study objective	6
	1.1.1 Primary Objective	6
	1.2 Study Design	6
2	Treatment Assignment	6
3	Randomization and Blinding Procedures	6
4	Interval Windows	6
5	Levels of Significance	7
6	Analysis Sets	7
7	Sample Size Justification	7
8	Statistical Analysis Methods	7
	8.1 General Conventions	7
	8.2 Disposition of Study Subjects	8
	8.3 Demographic and Baseline Characteristics	8
	8.4 Endpoint(s) <i>and Associated Hypotheses</i>	8
	8.4.1 Primary Endpoint	8
	8.4.2 Secondary Endpoints	9
	8.5 Analysis of Primary Endpoint	10
	8.6 Analysis of Secondary Endpoints	11
	8.6.1 Plans for Interim Analysis	12
	8.6.2 Plans for Final Analysis	12
	8.7 Sensitivity Analyses	12
	8.8 Subgroup Analyses	12
	8.9 Assessment of Site Homogeneity	12
	8.10 Exploratory Analyses	13
	8.11 Handling of Missing Data	13
	8.12 Adjustments for Multiplicity	13
	8.13 Safety Analyses	13

	8.14 Additional Endpoint Analyses.....	14
9	Data Monitoring Committee (DMC).....	14
10	Appendix: Tables, Listings and Graphs Shells	14

1 Introduction

1.1 Study objective

1.1.1 Primary Objective

The primary objective of this registry is to compile data that will be analyzed at various timepoints, to understand the impact of selected parameters on procedure and patient outcomes. The database will capture data related to (1) Ablation Procedure parameters, (2) Patient parameters, and (3) Healthcare Provider parameters.

1.2 Study Design

This is a multicenter, observational registry that follows patients for a total of up to 5 years from the date of the first liver ablation procedure with either the NEUWAVE Microwave Ablation System or the NEUWAVE Microwave Ablation System with Ablation Confirmation.

This is an “umbrella registry,” which was included as an optional component in other NEUWAVE studies; hence, data from consenting patients who are or will be enrolled in other NEUWAVE soft tissue liver lesion ablation studies will be included in this registry. All other patients will be enrolled and followed prospectively, enrolled retrospectively with prospective, longitudinal follow up, or enrolled retrospectively with all retrospective follow up.

2 Treatment Assignment

This is a single-arm registry where all enrolled patients will be ablated using the NEUWAVE Microwave Ablation System as part of the site’s SOC treatment or per protocol for those patients who are also enrolled in other NEUWAVE studies.

3 Randomization and Blinding Procedures

As this is a single-arm registry, no randomization will occur, and no blinding procedures are required.

4 Interval Windows

Interval windows are provided in the Schedule of Assessments section of the study protocol. No additional windows are planned for analysis purposes.

5 Levels of Significance

No levels of significance are specified as no specific hypotheses about any of the outcomes of interest are being formulated or tested. Two-sided 95% confidence intervals (CI) will be estimated for specific endpoints for descriptive purposes only.

6 Analysis Sets

All Enrolled Set (AES): Consists of subjects who signed informed consent form or retrospectively enrolled with a waiver for signing informed consent form. The AES will be used for disposition of study subjects.

Full Analysis Set (FAS): FAS Consists of subjects who met inclusion/exclusion criteria and to whom the NeuWave Ablation device was utilized during procedure. Primary and secondary endpoints will be analyzed using FAS.

Safety Analysis Set (SAF): SAF Consists of subjects who met inclusion/exclusion criteria and to whom the NeuWave Ablation device was utilized during procedure. Safety endpoints will be analyzed using SAF.

7 Sample Size Justification

This registry will be open to receiving data from all patients who are ablated with microwave ablation of soft tissue liver lesions using the NEUWAVE Microwave Ablation System. Given that the objective of the registry is to investigate the relationships that exist between the stated clinical outcomes, patient and provider parameters, and microwave ablation (MWA) time and power, no power analysis or sample size determination have been performed given the absence of a specific hypothesis to test.

8 Statistical Analysis Methods

8.1 General Conventions

Data will be summarized in tables and further details at a granular-level data will be provided in listings.

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 total and counts for each category and their corresponding percentages.

Data recorded at the nominal visits or unscheduled visits will be presented in summary tables; however, data captured at unscheduled visits will not be included

in “by visit” summary tables. Listings will include data for both scheduled and unscheduled visits.

Analyses will be conducted using SAS version 9.4 or higher. During the course of statistical 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 table or 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, no amendment of the SAP will be 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.

8.2 Disposition of Study Subjects

Subject disposition will be summarized using counts and percentages. The number and percentage of subjects screened, enrolled, completed, and discontinued will be tabulated along with the specific reasons for discontinuation (CRF page Subject Completion/Discontinuation).

8.3 Demographic and Baseline Characteristics

Summary statistics will be provided for subject demographics (age, childbearing potential, race, and ethnicity), vital signs that include height, weight, and BMI, and smoking history. Listings will be presented for subject’s inclusion/exclusion criteria, demographic and baseline characteristics.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. A listing will be presented for medical history. Surgical history, treatment history, and concomitant medications will be listed only.

8.4 Endpoint(s) and Associated Hypotheses

There will be no hypothesis testing conducted for the primary or secondary endpoints. Two-sided 95% CIs will be estimated for selected endpoints for descriptive purposes.

8.4.1 Primary Endpoint

Perioperative endpoint-

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 (i.e., the ablation zone completely overlaps or

encompasses the target lesion(s) plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure. Technical Success is assessed at Visit 2 following the ablation of the target lesion.

Short term endpoint -

2. Technique efficacy, ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (i.e., the ablation zone completely overlaps or encompasses the target lesion(s) plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, at Visit 3 (between 7 days and less than 3 months post-ablation).

Long term endpoint -

3. Target lesion recurrence (local recurrence) rate evaluated at every visit starting from visit 4 after the primary ablation at visit 2 of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

8.4.2 Secondary Endpoints

Secondary endpoints of this registry are:

1. Secondary efficacy rate, defined as the percentage of soft tissue lesions that have undergone successful repeat ablations (target or non-target) following identification of local soft tissue lesion progression. A successful repeat ablation will be defined as ablation of the lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (i.e. the ablation zone completely overlaps or encompasses the lesion plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure.

2. Regional recurrence rate at a separate location in the liver (outside the initial treatment site(s)), evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

3. Recurrence-free survival, evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

4. Overall survival, evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up.
5. Assess economic impact of ablation by capturing procedure-related items such as: complete procedure duration, ablation duration, number of ablations, length of hospital stay, and number and types of probes used.
6. Incidence of adverse events (AEs) (SAEs) that are deemed at least unlikely related to the procedure or device and all serious adverse events (SAEs) from the start of the ablation procedure through the end of the study.
7. Two QOL questionnaires: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and liver-specific QLQ-HCC18.

Note: These two questionnaires were chosen as tools to assess overall health status/quality of life in the patient population with soft-tissue liver lesions.
8. Numeric Pain Rating Score.

8.5 Analysis of Primary Endpoint

The number and percentage of patients and lesions achieving technical success will be summarized and a two-sided 95% confidence interval will be provided based on Clopper-Pearson's method. Technical success is achieved when the ablation is defined as a complete ablation by the performing physician. Technical success will be summarized at patient level and at lesion level. Technical success is achieved for a patient when all ablated lesions are defined as a complete ablation by the performing physician.

The number and percentage of patients and lesions achieving technique efficacy will be summarized and a two-sided 95% confidence interval will be provided based on Clopper-Pearson's method. Technique efficacy is achieved when the ablation is defined as a complete ablation by the performing physician. Technique efficacy will be summarized at patient level and at lesion level. Technique efficacy is achieved for a patient when all ablated lesions are defined as a complete ablation by the performing physician.

Target lesion recurrence will be summarized at patient level and at lesion level. Time-to-event analysis (survival analysis) using Kaplan-Meier's method will be utilized to estimate the target lesion recurrence rate at 3-month, 6-month, up to 60-month follow up. Cumulative incidence rate will be estimated for target lesion recurrence considering death as a competing risk and estimates will be presented at 3-month, 6-month, up to 60-month follow up. A two-sided 95% CI will be estimated for target lesion recurrence. Subjects who failed technique efficacy will be excluded from the analysis for target lesion recurrence.

First occurrence of a target lesion recurrence at patient level will be considered as the “event” for time-to-event analysis.

First occurrence of a target lesion recurrence at lesion level will be considered as the “event” for time-to-event analysis.

8.6 Analysis of Secondary Endpoints

The number and percentage of patients and lesions achieving secondary efficacy will be summarized and a two-sided 95% confidence interval will be provided based on Clopper-Pearson’s method. Analysis for secondary efficacy rate includes only repeat ablations for target and non-target lesions.

For patient level analysis – secondary efficacy is achieved for a patient when all re-ablations of target lesions and all re-ablations of non-target lesions are defined as a complete ablation by the performing physician. The denominator for subject level analysis will include subjects who had a re-ablation during visit 3 to visit 14 including unscheduled visits.

For lesion level analysis – secondary efficacy is achieved for a lesion when all repeat ablations of that lesion (target and non-target lesions) are defined as complete ablation by the performing physician. The denominator for lesion level analysis will include lesions that had a repeat ablation during visit 3 to visit 14 including unscheduled visits.

Regional recurrence rates will be estimated at patient level. Time-to-event analysis (survival analysis) using Kaplan-Meier’s method will be utilized to estimate the regional recurrence rate at 3-month, 6-month, up to 60-month follow up. Two-sided 95% CI will be estimated for regional recurrence rate. First occurrence of identification of a new lesion outside the initial treatment site(s) during visit 3 to visit 14 including unscheduled visits at patient level will be considered as the “event” for time-to-event analysis at patient level.

Recurrence-free survival rates will be estimated at patient level. Time-to-event analysis (survival analysis) using Kaplan-Meier’s method will be utilized to estimate the recurrence-free survival rate at 3-month, 6-month, and up to 60-month follow up. Two-sided 95% CI will be estimated for recurrence-free survival rate.

An “event” is defined for recurrence-free survival if any of the following conditions are met:

- a. First occurrence of a target lesion recurrence during visit 4 to visit 14 including unscheduled visits at patient level
- b. Identification of a new non-target lesion during visit 3 to visit 14 including unscheduled visits at patient level

c. Deaths from any cause of a patient during the follow up period

Overall survival rate will be estimated at 3-month, 6-month, and up to 60-month follow up using Kaplan-Meier's method. Two-sided 95% CI will be estimated for overall survival rate.

Scores from the EORTC QOL questionnaires and Numeric Pain Rating Scales will be summarized with methodology consistent to the recommendations of the specific survey. Economic impact of ablation by capturing procedure-related items will be summarized with descriptive statistics.

Incidence of adverse events (AEs) (SAEs) that are deemed at least unlikely related to the procedure or device and all serious adverse events (SAEs) from the start of the ablation procedure through the end of the study will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

8.6.1 Plans for Interim Analysis

There are no plans for interim analyses with an intent to stop the registry early or to adapt the registry design or planned number of patients.

8.6.2 Plans for Final Analysis

Final analysis will be conducted after the database lock takes place for the study.

8.7 Sensitivity Analyses

No sensitivity analysis will be conducted.

8.8 Subgroup Analyses

Subgroup analyses will be performed for the following variables: Type of disease (CRLM, HCC, Cholangiocarcinoma, Other) and NeuWave ablation confirmation software use. Subgroup analysis will be conducted for the primary endpoints that include technical success, technique efficacy, and target lesion recurrence.

8.9 Assessment of Site Homogeneity

Not applicable.

8.10 Exploratory Analyses

Logistic regression analysis will be utilized to explore the relationship between dichotomous clinical outcomes (technical success and technique efficacy) and ablation procedure, patient, and provider parameters. Significance level of 0.2 will be used for variable selection in a regression model. Cox proportional hazard model will be used for time to event analyses for target lesion recurrence to explore the relationship with ablation procedure, patient, and provider parameters.

8.11 Handling of Missing Data

Missing data will not be imputed.

8.12 Adjustments for Multiplicity

Not applicable.

8.13 Safety Analyses

All AEs reported during the study will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Separate summaries will be provided for device-related and procedure-related AEs. Serious AEs will be summarized in a similar manner. All reported adverse events will be listed.

Ninety-five percent confidence intervals may be provided for pre-specified adverse events of interest, which are:

- Ascites (accumulation of fluid causing abdominal swelling)
- Biloma/bile leak (buildup of bile within the abdomen)/bile leak)
- Bile duct injury
- Bleeding requiring transfusion, embolization (obstructing of blood vessel or organ to stop bleeding), or prolonged hospital stay
- Intrahepatic hematoma
- Pneumothorax and hemothorax
- Organ injury other than the liver (such as gastrointestinal injury/perforation, diaphragmatic injuries/hernia)
- Fever
- General feeling of tiredness
- Infection
- Liver dysfunction
- Liver abscess
- Nausea
- Pain
- Pneumonia
- Pleural effusion

- Post ablation syndrome, which is your body's response to the destroyed lesion. You may experience flu-like symptoms, including fever, decreased appetite, and general discomfort. This syndrome generally happens 3 to 5 days after the ablation procedure.
- Skin burn
- Thrombosis (local coagulation or clotting of the blood in the circulatory system, with/without tube drainage)
- Tumor implantation

8.14 Additional Endpoint Analyses

Not applicable.

9 Data Monitoring Committee (DMC)

Not applicable.

10 Appendix: Tables, Listings and Graphs Shells

Table shells are provided in a separate document for all summaries to be generated for this study. These shells are a guide to the general layout of data to be presented. Minor modifications can be made to suit existing programs or macros that are available. Additionally, a list of all listings to be created is provided corresponding to the eCRFs that are used in this study. All fields collected will be listed.

Signature Page for VTMF-24375215, V-TMF Version: 1.0
NEU_2017_04---Statistical Analysis Plan-30 Oct 2025

