SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: MarginProbe System

Device Trade Name: MarginProbe System

Device Procode: OEE

Applicant's Name and Address:

Dune Medical Devices, Inc.
111 Speen St, Suite 101
Framingham, MA 01701
United States

Date of Panel Recommendation: June 21, 2012

Premarket Approval Application (PMA) Number: P110014

Date of FDA Notice of Approval: December 27, 2012

Expedited:

Granted expedited review status on April 29, 2011 because the device is 1st of a kind. It represents a breakthrough technology that may offer a clinically meaningful advantage in providing intraoperative indication of the margin status as an adjunct to standard of care during breast conserving surgery, lumpectomy procedures for breast carcinoma, which may be serious or life-threatening, or present a risk of serious morbidity.

II. INDICATIONS FOR USE

The Dune MarginProbe™ System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the main *ex-vivo* lumpectomy specimen following primary excision and is indicated for intraoperative use, in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed breast cancer.

III. CONTRAINDICATIONS

The Dune MarginProbe™ System should not be used:

- To replace standard tissue histopathology assessment
- On *ex-vivo* lumpectomy specimens that have been exposed to saline, ultrasound gel or local anesthetic solutions.
- On *in-vivo* tissue (i.e. it should not be used within the lumpectomy cavity)
- On tissues other than breast tissue (i.e. it should not be used on Sentinel Lymph Nodes)
- Closer than 1.5 mm to a fine needle localization guidewire

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Dune MarginProbe™ System labeling.

V. DEVICE DESCRIPTION

The Dune MarginProbe™ System utilizes RF spectroscopy to to measure the dielectric properties of *ex-vivo* breast lumpectomy tissue and to characterize it as malignant (positive) or normal (negative).

A. Overview

The MarginProbe System (see Figure 1) is a medical device, utilizing electromagnetic waves, comprised of a probe and a console that are packaged and sold separately.

- The console has a user interface system with display, audio components and operation buttons. There are three software components installed on the console of the MarginProbe System: the system main manager application software, the software that processes the calibration and classification, and the software for the RF interface between the probe and the console.

- The probe is a detachable, sterile, single-use, single-patient component. It is connected to the console by two RF cables and a vacuum tube, via a single connector.

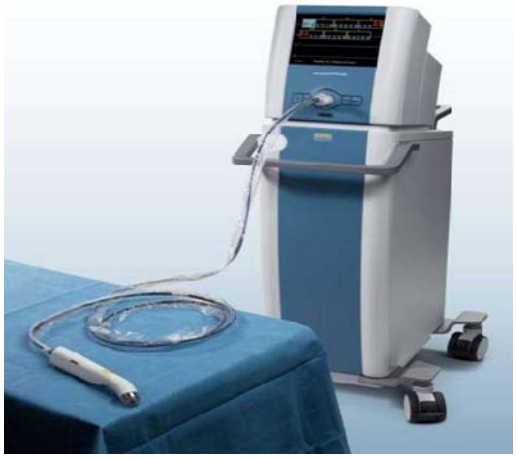


Figure 1 - MarginProbe™ System

The system block diagram (Figure 2) depicts the modules for two-way signal handling, including: generation and collection, a vacuum-based tissue attachment module, a memory module which stores data that enables characterization of tissue, a signal analysis software module, a classification software module which classifies the measured signals based on pre-established criteria, and a user interface module including display unit, an audio unit, and a control panel.

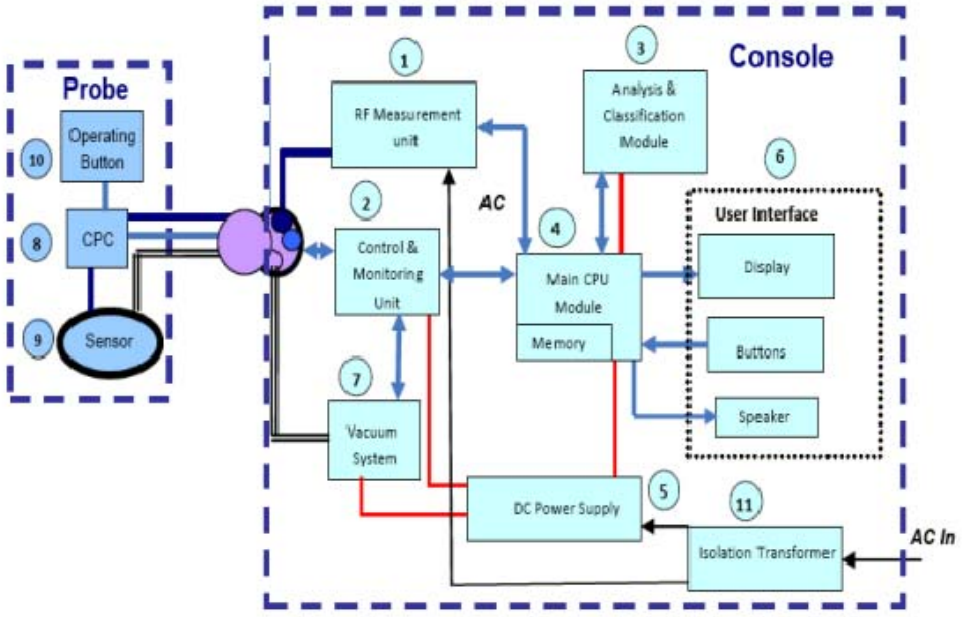


Figure 2 - System Block Diagram

The MarginProbe System Probe is used to sample the entire surface of the specimen (see Figure 3). Users are advised to take approximately 5-8 measurements per margin surface.

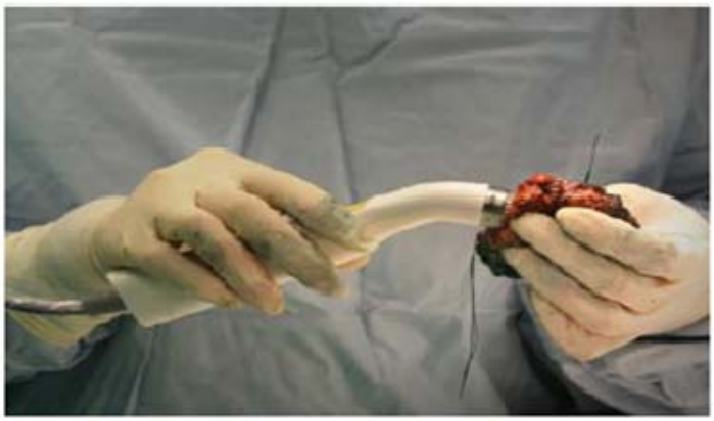


Figure 3 - Probe Applied to Tissue

Readings are displayed on the MarginProbe System Console as either positive or negative (see Figure 4).

If any one of the readings is positive, the *ex-vivo* lumpectomy margin should be considered positive, and an appropriate surgical action should be taken.

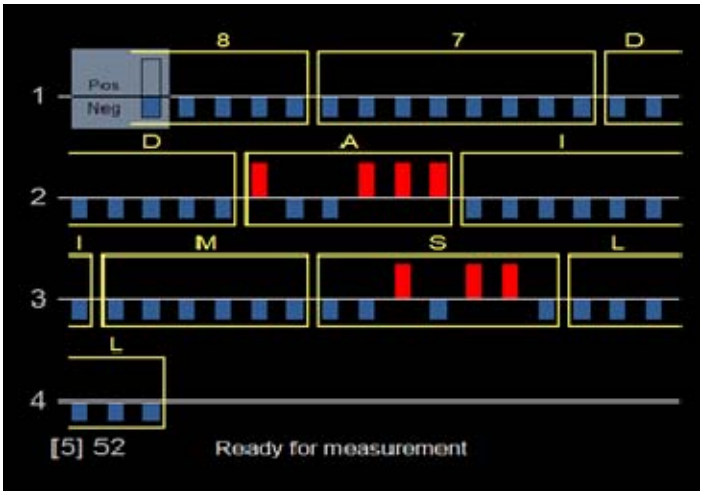


Figure 4 - Data Display on Console Screen

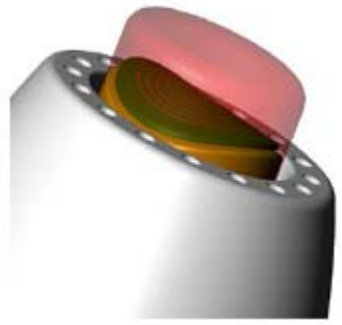
B. Design

The MarginProbe™ System is designed based on the principles of dielectric spectroscopy to characterize tissue. It applies an electric field to the tissue through a sensor mounted at

the tip of the probe and analyzes the reflection over wide range of RF frequencies. The sensor itself [the Fringe Field Sensor (FFS)] generates an oscillating transient electrical field in a small volume of tissue by employing the fringe field effect present at the edge of conductors.

The RF fields, which are applied locally, generate a transient electromagnetic field only in the immediate vicinity of the tissue touching the sensor. The volume of tissue in which this interaction occurs is about 100 mm^3. The energy applied per measurement is lower than 0.2 mJ. The power level in the immediate vicinity of the sensor is lower than 3 mW. This power level is sustained only during the short measurement time of 60 msec. The maximum voltage that the device can generate (P-P) at the tissue interface is 1.0 volts.

The probe has a footprint of 1.6 cm in diameter and effective measurement area of 7 mm. A light vacuum (0.4-0.6 ATM) secures the probe to the tissue and the sensor automatically moves into contact with the tissue. It applies an electric field to the tissue through a sensor mounted at the tip of the probe and analyzes the reflection over wide range of RF frequencies. The sensor itself [the Fringe Field Sensor (FFS)] generates an oscillating transient electrical field in a small volume of tissue by employing the fringe field effect present at the edge of conductors (see Figure 5).



- The sensor generates RF electromagnetic fields at 50MHz – 500MHz
- Measures a surface area of tissue 7 mm in diameter, adjacent to the sensor
- Low energy delivered to tissue (< 0.6 mJ)
- Fringe field resonating sensor. The sensor characteristics (e.g. frequency and amplitude) are dependent on tissue properties.
- The algorithm and clinical studies for MarginProbe™ device assessed lumpectomy tissue readings at the surface margins ≤ 1 mm in depth.

Figure 5 - Fringe Field Sensor (FFS) at Probe Tip

The FFS creates an electromagnetic field which is exponentially decaying in the tissue. The deterioration is by a factor of 0.379 (1/e) at ~ 1.5 mm of tissue penetration, and by a factor of 0.135 (1/e^2) at ~ 3 mm of tissue penetration. The field decays by approximately 60% through the first 1.5mm of tissue and by approximately 80% through the first 3mm of tissue.

The algorithm and clinical studies for MarginProbe™ device assessed lumpectomy tissue readings at the surface margins ≤ 1 mm in depth.

When a measurement is performed, reflected signals from the FFS are collected and analyzed by the system. The resonance frequency and the amplitude of the reflection change significantly with the change in tissue properties. An example of reflected waveforms is presented in Figure 6, which shows the different reflection profiles measured from confirmed malignant and normal tissue.

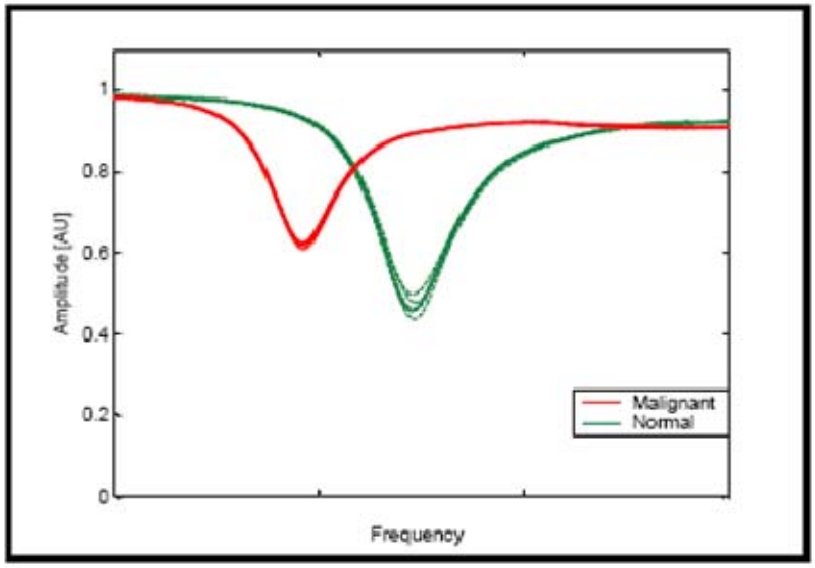


Figure 6 - Malignant and Non-Malignant Tissue Sensor Response

The sensor, by design, has a resonance frequency which depends on the properties of the material adjacent to its surface. Typically, the resonance frequency (the dip frequency) and the amplitude of the signal at this frequency will differ between cancerous and normal tissues. The positive/negative MarginProbe reading is achieved by applying a classification algorithm to determine if the tissue is malignant (Figure 7).

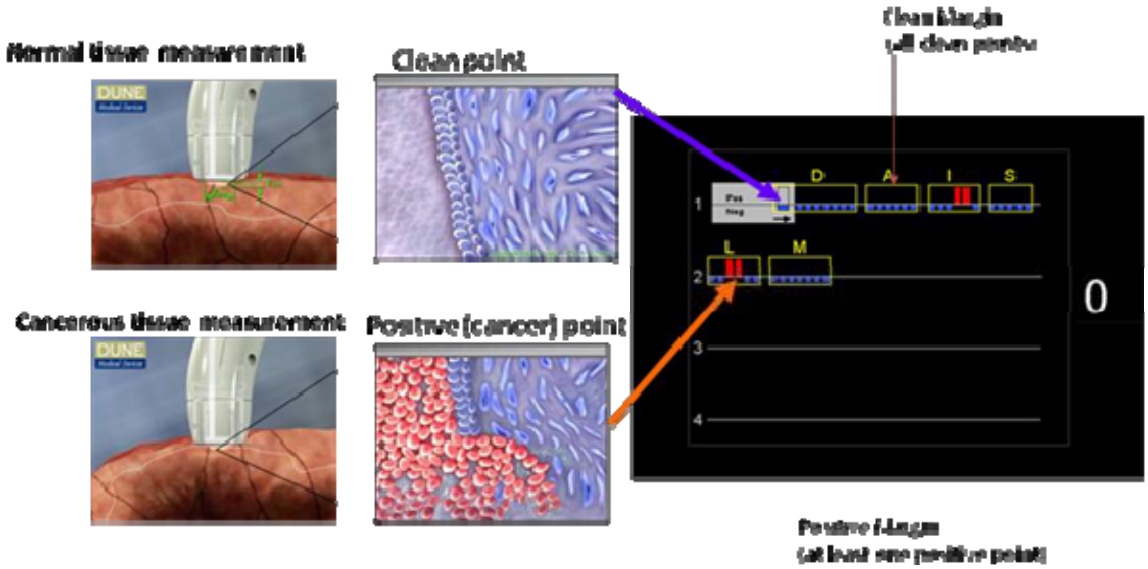


Figure 7: Classification of Tissue with the Dune MarginProbe™ System

C. Classification Algorithm

The algorithm is responsible for assigning the classification (i.e., cancer positive or cancer negative) of the tissue measurement. The positive or negative assignment is based on the impedance and frequency parameters of the measured signal when compared to a threshold derived from known values of cancerous and non-cancerous measurements in breast tissue. This signal is received by the software module which characterizes it by a set of parameters. As can be seen from Figure 8, the two main characteristics of the response signal are frequency at resonance (f0) and the amplitude at resonance (|R|dip).

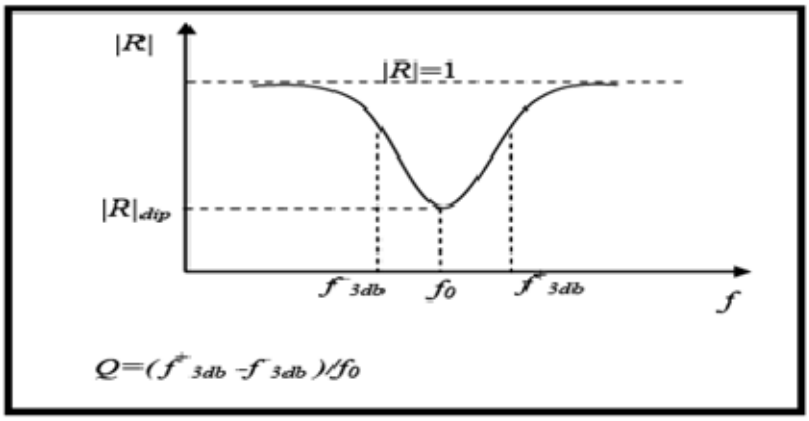


Figure 8 - Schematic Representation of the Sensor's Response

The classification algorithm is implemented on an embedded processor hardware system. The algorithm includes two types of data sets: one type to identify the best classifiers and the basic classification criteria at the point level, and a second type to fine-tune the

decision line based on comparison of margin (face) level data (device readings and histology).

The basic principle used for device development is the difference in dielectric properties between malignant and benign tissues. Two quantities are used to characterize the tissue adjacent to the probe sensor as malignant or benign: the resonant frequency (frequency at which the received signal amplitude reaches a minimum) and the impedance measured at that frequency. For each point measurement, i.e., for each measurement taken with the probe at a particular location, these two quantities can be plotted in a 2D space called the 2D phase space, as shown in Figure 9. The classification algorithm partitions the data points in the 2D phase space into two sets: one set that is called positive by the device, and the other set is called negative.

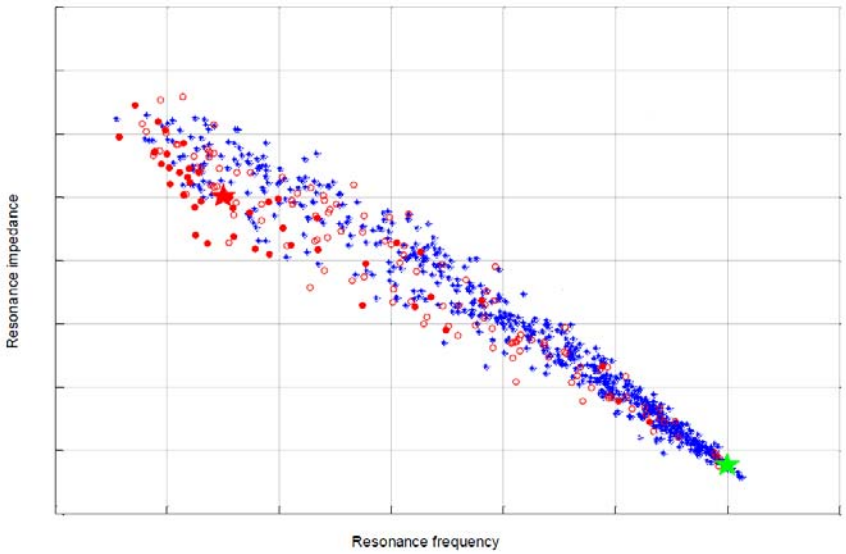


Figure 9 - The 2D Phase Space. Each point-level data is represented as a point in the 2D space of resonance frequency and impedance at resonance.

Data from malignant tissue are represented in red (solid red for cancer > 30%, and circle red for cancer ≤ 30%), and those from benign tissue are represented in blue. That the red and blue point clouds overlap--meaning that the device is not perfect in distinguishing between malignant and benign tissue.

D. Changes Between the Clinical and Commercial Product

The system used in the investigational study is named MarginProbe™ (MP) Type 1.0. In parallel, the sponsor developed and released a commercial version intended only for the EU market. This commercial system was modified later to be identical in performance and algorithm to the MP Type 1.0 system.

Compared to Type 1.0 used in the pivotal clinical trial, the MarginProbe™ System Type 1.1 has sustained development changes in the external appearance of the device, including reduction of the device weight.

For the console software, changes were made to: platform operating system; application software development tool and programming language; and addition of product use security features (limits to number of measurements and time for use).

For the probe, changes were made to: probe fabrication process (PCB connection with cables and O-ring assembly; nipple design (purchased part); cable connectors; CPC mechanics (Calibration module).

There were no changes to the device principles of operation or performance. In the disposable probe, all parts that contact the tissue remained the same. The sensor sensing element, attachment mechanism, user interface, and classification algorithm all remain identical to those in the MarginProbe System Type 1.0. There were no changes to the probe packaging and sterilization processing. Assessment of all these changes via verification and validation activities, as well as a system level test, demonstrated no impact on performance or use of the MarginProbe System.

Additionally, a system level equivalence test that was performed incorporated material samples representative of heterogeneous human breast tissue, including types of invasive and in situ cancers, fat, and normal tissues. The 236 different samples were selected randomly from all possible samples in the target breast tissue population to reflect the full range of possible sensor readings from lumpectomy specimens. The range of materials used in the test spans the full range of measurements on heterogeneous breast tissue lumpectomy specimens. This test demonstrated equivalence of the MarginProbe System Type 1.0 and MarginProbe System Type 1.1 as shown in Table 1.

In addition, a confirmatory equivalence study was conducted to compare the performance of the MarginProbe System Type 1.0 to MarginProbe System 1.1 using human breast tissue in which specific point measurements were made by each device type on both normal and malignant breast tissues. The testing was performed on more than 200 measurements, from 12 lumpectomy specimens. Three specimens had positive margins. Matched device readings using both systems demonstrate nearly perfect concordance between readings from the two versions of the MarginProbe System on lumpectomy specimens. These results further validate the equivalence between the two versions of the MarginProbe System and support the use of the pivotal trial results, conducted with MarginProbe System Type 1.0, to represent the performance expected from the commercially available MarginProbe System Type 1.1 device.

Table 1 - Summary of Equivalence Test Results

Test	Number of samples	Equivalence	Repeatability (Type 1.1)
Samples representative of heterogeneous breast tissue	236	99.1% (234/236) [95% CI: 97 – 100]	100% (236/236) [95% CI: 98.5 – 100]
Breast tissue	214	98.6% (211/214) [95% CI: 96.0 -	100% (214/214) [95% CI: 98.3-100]

		99.7]	

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative adjunctive diagnostic methods for identifying cancerous tissue at the margins of the *ex-vivo* lumpectomy specimen. Alternative procedures include gross examination of the *ex-vivo* lumpectomy specimen, palpation of the ex-vivo lumpectomy specimen, palpation of the lumpectomy cavity, lumpectomy specimen imaging by radiography, lumpectomy specimen imaging by ultrasound, frozen section analysis of the margins, and touch prep cytology of the margins. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method(s) that best meets expectations and lifestyle.

VII. MARKETING HISTORY

MarginProbe is commercially available in Germany, Switzerland, and Israel. MarginProbe has not been withdrawn from the market in any foreign market for reasons related to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Extension of procedure time
- Errors in device reading
- Unnecessary removal of healthy tissue with a potential negative impact on cosmetic results or cosmetic appearance.
- Infection
- Local tissue damage
- Bleeding

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. System Level Testing

System Level Testing was done for: safety, EMC, Immunity, software and hardware verification & validation, and performance equivalency between clinical and commercial systems. Testing for the system includes a console and a probe that met the established specifications for the planned commercial product.

These testings are summarized in Table 2.

Table 2 - Summary of System Level Testing

SYSTEM-LEVEL TESTING (CONSOLE + PROBE)	TEST SUBJECT	TEST RESULTS
Safety Test	Safety testing was performed, by the Standards Institution of Israel (SII) according to the IEC 60601-1 standard following the CB scheme procedure.	The MarginProbe System type 1.1 passed all tests.
EMC Test	Electromagnetic Compatibility testing was performed by the Standards Institution of Israel (SII), in accordance to the IEC 60601-1-2 standard.	Analysis of test results demonstrated that MarginProbe System Type 1.1 complies with IEC 60601-1-2 Electromagnetic Compatibility requirements.
RPT-R&D-00122 Immunity Test of Signal Characteristics	Immunity testing was performed to show that for the expected disturbance signal strengths the signal parameter deviations are small, such that system performance is not influenced. When the disturbing signal is very large, the measurement is disqualified.	The MarginProbe System is immune to strong CW radiation. A measurement disqualification was observed for large disturbing signals.
Software Verification	The verification tests encompass the system SW tests, regression tests, load tests and stress tests and are performed according to defined testing procedures.	The SW Verification results demonstrate all tests as 'passed,' therefore verification was completed successfully.
Software Validation	SW Validation tests software's functionality and performance.	The SW validation results demonstrate all tests as 'passed,' therefore validation was completed successfully.
HW-02-011 Hardware Verification	Verification tests were conducted on the system's hardware to verify that probe requirements, console requirements, probe user interface, console user interface and console maintenance, meet requirements set forth in the Design Input and Specification Documents.	All hardware verification tests for the MarginProbe System passed acceptance criteria and met required specifications.
RPT-R&D-00119 MarginProbe System Type 1.0 and Type 1.1 Equivalence Test	A system level test was performed to demonstrate that the performance of the MarginProbe System Type 1.1 (MP Type 1.1) and clinical system MarginProbe System Type 1.0 (MP Type 1.0) are identical.	Testing results on 236 samples representing heterogeneous breast tissue of varying tissue type composition demonstrated that the commercial product (MP Type 1.1) and the clinical product (MP Type 1.0) performance is the same.

SYSTEM-LEVEL TESTING (CONSOLE + PROBE)	TEST SUBJECT	TEST RESULTS
DD-RPT-0268 MarginProbe System Type 1.0 and Type 1.1 Equivalence Test on Tissue	A confirmatory equivalence study was conducted to compare the performance of the MarginProbe System Type 1.0 to MarginProbe System 1.1 using human breast tissue in which specific point measurements were made by each device type on both normal and malignant breast tissues.	The results of more than 200 matched device readings demonstrated nearly perfect concordance between readings from the two versions of the MarginProbe System on lumpectomy specimens. These results further validated the equivalence between the two versions of the MarginProbe System.

B. Console Level Testing

Console Level Testing was done for packaging, transportation, temperature, and environmental factors. The console used for testing met the specifications for the MarginProbe System commercial product.

Table 3 describes the tests performed and their results.

Table 3 - Summary of Console Level Testing

CONSOLE-LEVEL TESTING	Subject	Results
Environmental & Transportation Test	Environmental & Transportation tests were done to demonstrate the capability of the MarginProbe console packaging configuration to maintain the integrity of the package and product during storage, handling and transportation. Environmental and transportation testing were performed with MarginProbe System Type 1.5 which is slightly different than the MarginProbe System Type 1.1. Evaluation was done to confirm that there was no significant change done to the sub-components of the console when migrating from the previously tested system model to the new model MarginProbe System type 1.1 as detailed in DD-NTF-0098 Environmental Tests for MarginProbe™ Console. Therefore, there is no need to repeat the environmental testing	All results met acceptance criteria for the MarginProbe Type 1.5 console. Testing for MarginProbe System Type 1.5 also applies to the MarginProbe Type 1.1 console, meeting the requirements of IEC60721-4-2 & IEC60259 - environmental standards for transportation and storage.

CONSOLE-LEVEL TESTING	Subject	Results
	and the previous test report can be adopted to confirm the compliance of the new MarginProbe Type 1.1 console to the requirement of IEC60721-4-2 & IEC60259 environmental standards for transportation and storage.	

C. Probe Level Testing

Probe Level Testing was done for: Biocompatibility, Sterilization, Packaging, Shelf Life, and Environmental & Transportation. The probe used for testing met the established specifications for the MarginProbe System commercial product.

These testings are summarized in Table 4.

Table 4 - Summary of Probe Level Testing

PROBE-LEVEL TESTING	Subject	Results
DD-NTF-0110 MarginProbe Probe - Biocompatibility Testing	Biocompatibility tests for MarginProbe probe were performed by NAMSA labs (based on ISO 10993 requirements).	All tests passed acceptance criteria and met requirements.
DD-NTF-0158 Sterilization Validation of MarginProbe Probe	Sterilization of the MarginProbe probe by ethylene oxide was validated in accordance with current standards utilizing the conservative half-cycle method.	All results met the acceptance criteria
DD-NTF-0109 Packaging Validation for the MarginProbe Probe	The operation and performance of the blister sealing process was validated. The validation consisted of the installation and operational qualifications of the METEOR blister sealing machine installed in Dune and later in PMP clean rooms and the performance qualification of the sealing operation.	All packaging processes passed validation and met requirements.

PROBE-LEVEL TESTING	Subject	Results
EP-02-008 Shelf life Validation for MarginProbe Probe	Testing was done to demonstrate that the MarginProbe probe package is capable of maintaining the sterility of the device over its indicated shelf life period (per device labeling). In addition, the product was subjected to functionality tests per the study design. This study was designed to obtain supportive data from both accelerated and real time data.	Results show that sterility is maintained and the probe is functional. The MarginProbe probe can be labeled with an expiration date of 3 years from the production date.
Environmental & Transportation Testing of Probe	Testing was done to demonstrate the capability of the MarginProbe probe packaging configuration to maintain the integrity of the package and product during storage, handling and transportation. A series of stress tests were performed in accordance with IEC TR 60721-4-2. The packaging was subjected to temperature and humidity stresses, as well as vibration, shock and free fall stresses as part of the study.	The MarginProbe probe passed all test criteria.

X. SUMMARY OF THE MARGINPROBE SYSTEM PIVOTAL STUDY

Dune Medical Inc. performed a clinical pivotal study to establish a reasonable assurance of safety and effectiveness of the MarginProbe System. The MarginProbe System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the *ex-vivo* lumpectomy specimen following primary excision and is indicated for intraoperative use, in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed breast cancer in the US. The pivotal study was performed under IDE # G070182. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 2008 and March 2010.

The MarginProbe System pivotal study was a prospective, multicenter, randomized (1:1), controlled, double-arm study. Breast cancer patients were randomized to either receive standard

of care (SOC) lumpectomy or Standard of Care lumpectomy with adjunctive MarginProbe device use (SOC + Device) .

Key Aspects of the protocol are as follows:

1. Patient Study Inclusion and Exclusion Criteria

Enrollment in the pivotal study was limited to patients who met the following inclusion criteria:

- Women histologically diagnosed with carcinoma of the breast
- Women with non-palpable malignant lesions, requiring image guided localization.
- Undergoing lumpectomy (partial mastectomy) procedure.
- Age 18 years or more
- Signed informed consent form

Patients were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

- Multicentric disease (histologically diagnosed cancer in two different quadrants of the breast)
- Bilateral disease (diagnosed cancer in both breasts)
- Neoadjuvant systemic therapy
- Previous radiation in the operated breast
- Prior surgical procedure in the same breast
- Implants in the operated breast
- Pregnancy
- Lactation

2. Patient Treatment

Patients were first enrolled and taken to the operating room for resection of the main lumpectomy specimen. The main lumpectomy specimen and lumpectomy cavity palpation and related re-excisions were performed before patient randomization. For all main specimens, the center of each of the 6 margins was suture marked. Patient were then randomized to either the SOC or SOC+Device arm intraoperatively, immediately after the main lumpectomy specimen was excised, oriented, center marked, palpated, and additional palpation based re-excision performed.

For patients randomized to the SOC+Device arm the surgeon:

- Applied the MarginProbe device to each of the 6 faces of the excised main lumpectomy specimen—sampling 5 – 8 points (and up to 12 points for larger specimens). The points sampled were at both even evenly spaced and suspicious sites.
- Was required to react to Device feedback. A single positive reading on any margin classified that margin as positive and required the surgeon to remove additional tissue from that margin.

- Documented the reasons why additional margins were not re-exicised despite a positive MarginProbe device reading. For the purposes of CSR primary endpoint calculations, lumpectomy cavity shavings that were not possible due to physical limitations (proximity to the skin or pectoralis fascia) the margin was considered "addressed"
- Was instructed not to use the MarginProbe device on shavings from the lumpectomy cavity shavings (even if a shaving was taken prior to randomization)
- Was instructed not to use the MarginProbe device within the *in-vivo* lumpectomy cavity.
- Was instructed not the use the MarginProbe device on *ex-vivo* lumpectomy tissue that had been exposed to saline or ultrasound gel. It was however acceptable to use the MarginProbe device on *ex-vivo* lumpectomy tissue exposed to sterile water.
- Was instructed not to use the MarginProbe device in the 1.5 mm region of tissue surrounding a fine needle localization guidewire.

For both SOC and SOC+Device arm patients, lumpectomy specimens were imaged by ultrasound or radiography after randomization and device use. Additional lumpectomy cavity re-excisions were taken as deemed appropriate based on specimen imaging results. Figure 10 provides a diagrammatic representation of the study design.

Note that the study design allows for an additional option to perform lumpectomy cavity shavings in the SOC+Device arm (option for shaving at 3 time points) versus the SOC arm (option for shaving at 2 time points).

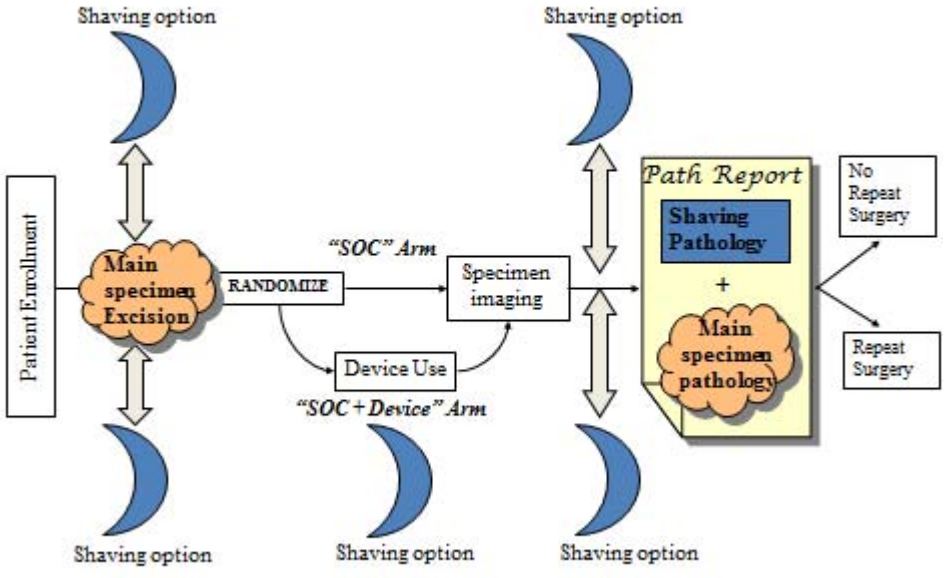


Figure 10 - Pivotal Study Study Design

The MarginProbe device was not used during lumpectomy reoperations.

The study consisted of two phases – a training phase and a randomization phase. Each surgeon had to complete the training phase before being able to randomize patients. Surgeons who had attended 2 or more device procedures (training or randomized) were certified in device use.

3. Pathology Protocol

Pathological assessment was standardized and identical for both study arms. Pathologists were blinded to randomization.

A positive margin was to be defined in this study as a margin microscopically measured and reported in the histopathology report to have cancer within 1 mm or less of the inked surface.

Each investigational site performed the histopathology assessment using a Standard Operating Procedure. Re-cut slides from the first 4 patients at each investigational site (Training, SOC, or SOC+Device) were to be sent to a core-lab and were to be used to review the accuracy and reporting capabilities of the investigational site pathology.

Dimensions (L, W, D) of all excised tissues were recorded. Tissue volume was determined by use of the ellipsoid formula:

$$V=(4/3)*\pi*L*W*D$$

4. Duration of Patient Follow-up

Patients were followed until the end of the lumpectomy procedure. Data were collected regarding all ipsilateral breast surgical procedures and their respective permanent histopathology data. Data were to be collected up until the earlier of the following events: conversion to mastectomy, initiation of chemotherapy or two months after the surgery date.

5. Study Endpoints

The prespecified study endpoints are as follows:

Safety evaluation consisted of assessment of all adverse events and serious adverse events, which were summarized using descriptive statistics.

The primary effectiveness endpoint (CSR) is measured as all pathologically positive margins on the main specimen being intraoperatively re-excised or "addressed". A re-excised or "addressed" margin does not mean that the final true outermost margin is pathologically negative for cancer.

- A positive margin is defined as a margin microscopically measured and reported in the histology report to have cancer within 1 mm or less of the inked margin.

- The main specimen is defined as the lumpectomy specimen removed prior to patient randomization. The main lumpectomy specimen does not include additional shavings even if the cavity shaving was performed prior to patient randomization.

- If a margin has been indicated as positive by the device and documented to not have been re-excised as required by protocol, due to resection already undermining the skin or reaching the pectoralis fascia, this margin will be counted as "detected" and "addressed" for the purpose of CSR endpoint calculation although it was not "re-excised".

An illustration of how CSR is determined is provided in Figure 11.

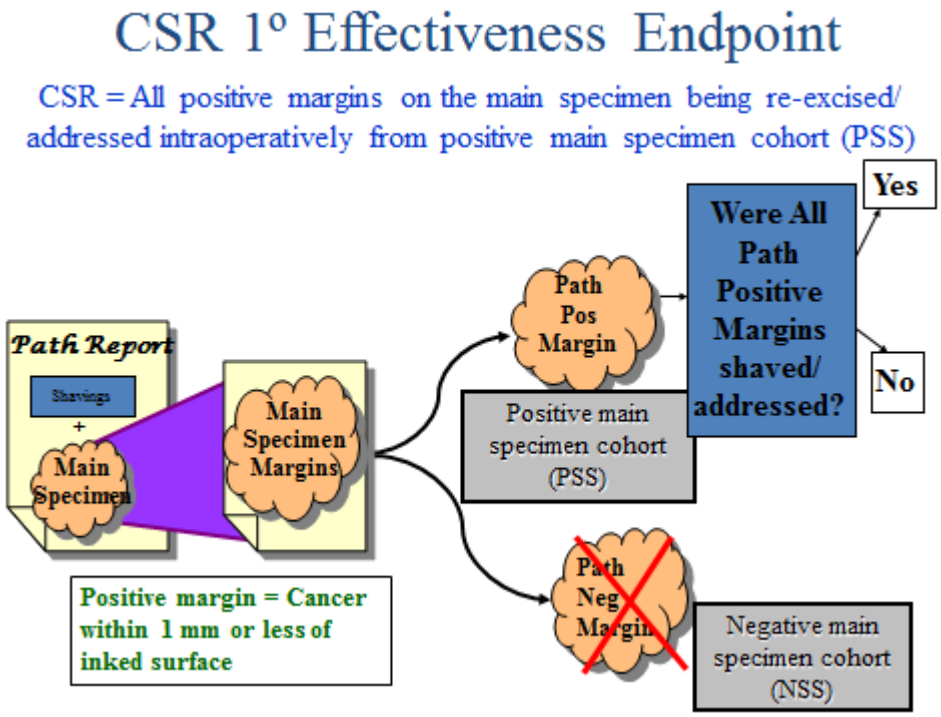


Figure 11 - Illustration of CSR Primary Endpoint

Figure 12 below illustrates how the CSR assessment includes both clinically relevant scenario which is the conversion of a specimen which has a pathologically positive for cancer margin to a specimen with negative for cancer margins and the clinically irrelevant scenario in which the additional shaving resulted in the true outermost margin of the specimen remaining pathologically positive for cancer.

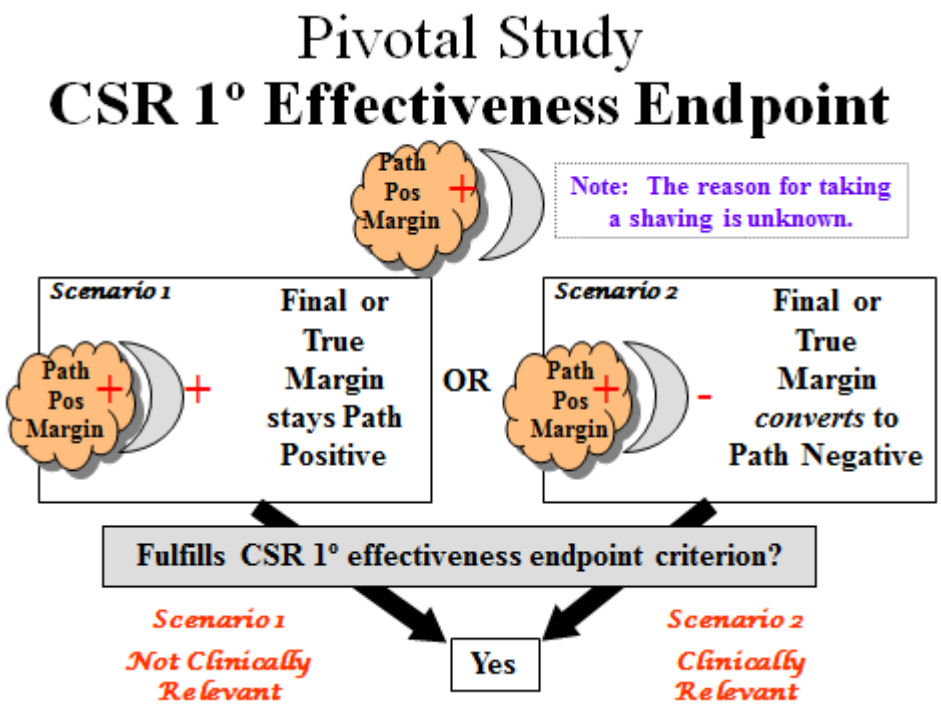


Figure 12 - CSR and Clinical Relevance

While CSR is a focused assessment that is limited to what is within the control of the MarginProbe device, there are limitations to the CSR primary effectiveness endpoint. Some of these limitations are present because the reason and timing for taking additional shavings of the lumpectomy cavity were not documented—that is, whether a shaving was taken because of clinical suspicion, imaging, other assessment, versus a positive MarginProbe device reading and whether the shaving was taken before randomization or after specimen imaging. While the device readings for each margin and the margins shaved were documented, the timing of each shaving and the reason prompting the shaving was not collected.

Table 5 summarizes the strengths and limitations of the CSR primary effectiveness endpoint for the pivotal study.

Table 5 - Strengths and limitations of the primary effectiveness endpoint, CSR

Strengths	Limitations
A focused assessment limited to what is within the control of the MarginProbe™ device i.e. causing additional cavity shavings.	The study design allows for an additional option to perform cavity shavings in the SOC+Device arm versus the SOC arm. The additional option in the SOC+Device arm may be responsible for an increase in CSR in the SOC+Device arm.

A by specimen assessment which does not give partial credit to intraoperative re-exision of some positive margins on the main specimen but not all positive margins on the main specimen.	The incremental contribution of the MarginProbe™ device to a higher CSR cannot be determined because the reason for taking a cavity shaving - i.e. SOC (clinical suspicion, or imaging) versus a positive MarginProbe™ reading - was not documented.
	Questionable clinical relevance. CSR considers whether a shaving was taken or not taken at positive margins on a lumpectomy specimen. CSR does not consider whether the shaving taken converted the initially positive for cancer margin to a negative for cancer final margin.
	CSR does not penalize false positive MarginProbe™ readings in the positive main specimen cohort. False positive MarginProbe™ readings in the positive main specimen cohort cause the resection of healthy tissue.
	CSR does not consider false positive MarginProbe™ readings in the negative main specimen cohort. False positive MarginProbe™ readings in the negative main specimen cohort cause the resection of healthy tissue.

Secondary effectiveness endpoints are summarized in Table 6 below.

Table 6 - Secondary Effectiveness Endpoints

Endpoint	Definition
Incomplete Surgical Re-excision	Proportion of patients with at least 1 positive margin not resected/addressed. Differs from primary effectiveness endpoint, CSR, since Yes/No definitions are opposite. Differs from the CSR endpoint since it is calculated from the AVS dataset rather than the PSS dataset.
Full Detection	Rate of patients with all positive margins on main specimen detected by device

Re-excision Procedure Rate	Rate of repeated ipsilateral breast surgical procedures (including mastectomies)
Positive Margin Presence	Rate of patients with at least 1 positive margin remaining after lumpectomy
TTV excised in the primary lumpectomy procedure (cm^3)	Average volume of total amount of tissue excised in lumpectomy

6. Pre-Specified Analysis Plan

For the primary efficacy analysis, a sample size of 116 valid primary effectiveness patients per arm was determined to provide at least 90% power to demonstrate superiority of SOC+Device over SOC.

The analysis populations are defined in Table 7.

Table 7 - Analysis Populations

Analysis Population	Definition
All Valid Subjects (AVS)	The AVS subjects included all randomized patients with valid histology data (and valid MarginProbe System data in Device arm)
Positive Specimen Subjects (PSS)	The PSS subject is a subset of the AVS Analysis Set of subjects with at least 1 histologically positive main specimen margin at depth ≤1 mm
Negative Specimen Subjects (NSS)	The NSS subject is a subset of the AVS Analysis Set of subjects with no histologically positive main specimen margin at depth ≤1 mm.

Safety was assessed using the AVS population. The primary effective endpoint was based on PSS population, and the secondary effectiveness endpoints were based on AVS, PSS or NSS populations as shown in Tables 8 and 9.

Table 8 - The Primary Effectiveness Endpoints Population

Endpoint	Analysis Population	Scoring
CSR	PSS analysis set	Complete Surgical Re-excision (CSR) was scored dichotomously as follows: No: At least one positive margin on the main specimen not re-excised/addressed intraoperatively. Yes: All positive margins on the main specimen re-excised/addressed intraoperatively

Table 9 - The Secondary Effectiveness Populations

Endpoint	Analysis Population	Scoring
Incomplete Surgical Re-excision	AVS analysis set. The groups were compared using 2-sided Fisher's Exact Test.	Incomplete Surgical Re-excision ("re-excision is used to mean "resection) was scored dichotomously: Yes: If at least 1 positive margin with d ≤ 1 mm on the main specimen was not resected/addressed intraoperatively. No: Otherwise This endpoint differed from the primary effectiveness endpoint, Complete Surgical Resection, since the Yes/No definitions were opposite.
Full Detection	PSS analysis set A 2-sided exact binomial 95% CI for the proportion of "Yes".	Scored dichotomously for SOC+Device arm patients only: Yes: If all positive margins on the main specimen with d ≤ 1 mm were detected by the device (in Device arm) No: Otherwise
Re-excision Procedure Rate	AVS analysis set Compared the groups using a Poisson regression model.	Number of repeated ipsilateral breast surgical procedures (including mastectomies) for each patient. This endpoint was counted as an integer per patient; the count was increased by 1 with each subsequent surgery.
Positive Margin Presence	AVS analysis set Compared the groups using a Poisson regression model.	Scored dichotomously. Yes: If there was at least 1 positive margin with d ≤ 1 mm after the first lumpectomy No: Otherwise
TTV excised in the	NSS analysis set	Total amount of tissue excised

primary lumpectomy procedure (cm^3)	Compared the groups using a 2-sided Wilcoxon Rank-Sum Test.	during lumpectomy for each patient.

The margin-level and patient level (ignoring location) sensitivity and specificity are reported for diagnostic performance of the MarginProbe device. These were not pre-specified in terms of an acceptable minimal sensitivity and specificity. The results here are based on the observed performance in the clinical pivotal study.

B. Subject Accountability

A total of 664 patients who were eligible for study enrollment underwent surgery and were allocated to either the roll-in group or randomization (enrollment allocation). Sixty-eight women were operated on in the roll-in phase and 596 were randomized equally to the Control (SOC arm) and Device treatment (Device +SOC arm) groups. All 664 women completed the study. Subject accountability is displayed below in Table 10.

Table 10 - Patient Accountability, Pivotal Study

Disposition	**Total n (%)**
Eligible for Participation	721
Did Not Enter Study	57 (7.9)
Failed eligibility	25 (3.5)
Withdrew consent	6 (0.8)
Other	26 (3.5)
Eligible for Allocation	664 (92.1)
Allocated to Enrollment	664 (100)
Roll-in	68 (10.2)
Randomized to Treatment	596 (89.8)
Device	298 (44.9)
Control	298 (44.9)
Completed Study	664 (100)
Did Not Complete	0 (0)

All 664 women were included in the Safety analysis set. The AVS analysis set includes 596 randomized (298 Device and 298 Control) patients and differs from safety analysis set in 64 roll-in women, as shown in Table 11.

Table 11 - Data Sets Analyzed: Number of Patients

Analysis Set	Patients Included	Treatment Group			Total n (%)
		Device n (%)	Control n (%)	Roll-In n (%)	
Safety Set	All patients for whom surgical procedure was initiated	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)
Effectiveness Sets					
AVS	All Randomized Patients	298 (100.0)	298 (100.0)	NA	596 (100.0)
PSS	Positive Specimen Patients	163 (54.7)	147 (49.3)	NA	310 (52.0)
NSS	Negative Specimen Patients	135 (45.3)	151 (50.7)	NA	286 (48.0)

All randomized patients completed the study protocol. There was no loss to follow-up in the study. There was no missing data related to the CSR endpoint; 38/1788 (2%) of margins were not measured by the device.

C. Demographics and Baseline Characteristics

Demographic characteristics were similar for the Device and Control groups. Overall, the groups appeared to be comparable. as shown in Table 12 and 13.

Table 12 - Demographics by Treatment Group

Parameter	Roll-In N=68	Treatment Group: Device N=298	Treatment Group: Control N=298
Ethnic Origin n (%)			
White[a]	59 (86.8)	250 (83.9)	260 (87.2)
African-American or Black	5 (7.4)	22 (7.4)	17 (5.7)
Asian	2 (2.9)	12 (4.0)	10 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0)	3 (1.0)	1 (0.3)
Other	2 (2.9)	11 (3.7)	10 (3.4)

[a] Includes Hispanics.

Table 13 - Baseline Characteristics by Treatment Group

Parameter	Roll-In N=68	Treatment Group: Device N=298	Treatment Group: Control N=298
Age (yrs) Mean (SD)	63.6 (11.1)	60.3 (11.4)	60.2 (11.1)
BMI (mean)	28.0	27.9	28.6
Bra Cup Size n (%)			
AA	0 (0.0)	2 (0.7)	4 (1.3)
A	6 (8.8)	16 (5.4)	16 (5.4)
B	21 (30.9)	101 (33.9)	73 (24.5)
C	24 (35.3)	99 (33.2)	93 (31.2)

Parameter		Treatment Group	
	Roll-In N=68	Device N=298	Control N=298
D	12 (17.6)	62 (20.8)	92 (30.9)
E	1 (1.5)	2 (0.7)	5 (1.7)
F	1 (1.5)	1 (0.3)	1 (0.3)
>F	1 (1.5)	1 (0.3)	2 (0.7)
Unknown	2 (2.9)	14 (4.7)	12 (4.0)

Table 14 presents the number of patients with a diagnosis, requiring that certain categories be combined. For patients with invasive types of carcinoma the mixed invasive category was used, and for patients with more than 1 diagnosis who did not have more than one type of invasive carcinoma, the mixed category was used. The treatment groups appear to be similar with respect to diagnosis.

Table 14 - Patient Diagnosis by Treatment Group (Per-diagnosis Analysis)

Patient Diagnosis	Treatment Group			All
	Device	Control	Roll-In Phase	
	N (%) Patients	N (%) Patients	N (%) Patients	N (%) Patients
Invasive Ductal Carcinoma	24 (8.1)	22 (7.4)	7 (10.3)	53 (8.0)
Invasive Lobular Carcinoma	26 (8.7)	13 (4.4)	2 (2.9)	41 (6.2)
Mixed Invasivea	8 (2.7)	5 (1.7)	1 (1.5)	14 (2.1)
Ductal Carcinoma in Situ	83 (27.9)	78 (26.2)	19 (27.9)	180 (27.1)
Tubular Carcinoma	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Mucinous Carcinoma	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)
Mixedb	155 (52.0)	179 (60.1)	39 (57.4)	373 (56.2)
Total	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

a Mixed invasive=Invasive Ductal Carcinoma+Invasive Lobular Carcinoma.
b Mixed=more than 1 diagnosis and not only invasive carcinoma.

Tumor stage results are presented in Table 15 below. The majority of patients were diagnosed with stage II breast cancer and below.

Table 15 - Tumor Stage

Treatment Group	0		I		II		III		IV		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Device	81	27.2	155	52.0	51	17.1	4	1.3	1	0.3	6	2.0	298	100.0
Control	84	28.2	161	54.0	44	14.8	6	2.0	0	0	3	1.0	298	100.0
Roll-In Phase	21	30.9	34	50.0	12	17.6	1	1.5	0	0	0	0	68	100.0
All	186	28.0	350	52.7	107	16.1	11	1.7	1	0.2	9	1.4	664	100.0

Receptor status is presented in Table 16. There were 84 subjects in device and control arms, and 19 in the roll-in subjects, for which HER2 status was not preformed.

Table 16 - Receptor Status

Receptor Status	Roll-In N=68	Device N=298	Control N=298
ER+	60/68 (88.2)	251 (84.2)	258(86.6)
PR+	52/68 (76.4)	223 (74.8)	217 (72.8)
HER2+	3/49 (6%)	20/214 (9%)	33/214 (15%)
HER2-	42/49 (85%)	175/214 (82%)	163/214 (76%)

D. Surgical Procedure

The mean duration of anesthesia time (hours: minutes) was 2:03 for the Device group, 1:52 for the Control group and 2:11 for the Roll-in group. This time includes surgical procedures, resections, completion of the protocol procedures, and device use. The mean duration of device use was 5 minutes for the Device group and 6 minutes for the Roll-in group.

Table 17 presents the number and percent of patients with a palpable tumor excised during lumpectomy. While all patients had non-palpable lesions at screening (inclusion criteria), the lesion may or may not have been palpable in the *ex-vivo* lumpectomy specimen.. There were no apparent differences between treatment groups with respect to palpable tumors during excision.

Table 17 - Frequency Distribution of Palpable Tumor during Lumpectomy by Treatment Group

Was The Tumor Palpable in The Excised Specimen?	Treatment Group			All
	Device	Control	Roll-In Phase	
	N (%) Patients	N (%) Patients	N (%) Patients	N (%) Patients
No	196 (65.8)	188 (63.1)	43 (63.2)	427 (64.3)
Yes	102 (34.2)	110 (36.9)	25 (36.8)	237 (35.7)
Total	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

Source: Statistical Table M-38 in Appendix 10.2.2.

Various intraoperative evaluations were used at surgeon discretion in both the SOC and SOC+Device arms and included radiological exam, ultrasound, ultrasonic guidance, touch cytology, gross assessment, and frozen section.

The reason for performing a lumpectomy cavity shaving—that is, whether a shaving was prompted by gross visualization/palpation, positive MarginProbe device readings, imaging, touch prep cytology or frozen section analysis--was not documented.

The methods of excision used during lumpectomy included the following: electrocautery, sharp excision, and scissors.

Table 18 describes number of patients undergoing SLNB with dye or radioisotope or both.

Table 18 - Number of Patients undergoing SLNB with Dye or Radioisotope or Both

	Roll-In N=68	Device N=298	Control N=298
SLNB performed	59 (72%)	223 (75%)	225 (75)

E. Pathology

Table 19 presents weight and volume of the main specimen. There were no apparent differences between treatment groups with respect to weight and volume of the main specimen. The mean size (diameter) of the main specimen was 4.85 cm for the Device group, 4.89 cm for the Control group, and 4.7 cm for the Roll-in group.

Table 19 - Descriptive Statistics of Specimen Weight and Volume by Treatment Group

Specimen Parameter	Treatment Group						All	
	Device		Control		Roll-In Phase			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Weight (g)	294	51.4 (42.2)	290	55.8 (49.8)	67	48.6 (69.4)	651	53.0 (49.0)
Volume (cm^3)	296	59.7 (51.4)	298	61.3 (52.5)	68	54.6 (67.5)	662	59.9 (53.7)

Source: Statistical Table M-46 in Appendix 10.2.2.

Overall mean tumor size was similar for the groups (MarginProbe=1.7 cm^3, Control=1.6 cm^3).

The tumor type (as assessed by post-operative histopathology) by treatment group are presented in Table 20. The treatment groups appear to be similar with respect to tumor type. The number of positive margins on the main specimen, by treatment group, also appears to be similar.

Table 20 - Frequency Distribution for Tumor Type by Treatment Group

Tumor Type	Treatment Group			All
	Device	Control	Roll-In Phase	
	N Specimens (%)	N Specimens (%)	N Specimens (%)	N Specimens (%)
Invasive ductal carcinoma	158 (53.0)	179 (60.1)	40 (58.8)	377 (56.8)
Invasive lobular carcinoma	46 (15.4)	26 (8.7)	9 (13.2)	81 (12.2)
Ductal carcinoma in-situ	207 (69.5)	229 (76.8)	46 (67.6)	482 (72.6)
Tubular Carcinoma	5 (1.7)	6 (2.0)	2 (2.9)	13 (2.0)
Mucinous Carcinoma	10 (3.4)	3 (1.0)	2 (2.9)	15 (2.3)
Medullary Carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary Carcinoma	0 (0.0)	2 (0.7)	1 (1.5)	3 (0.5)
Non malignant (NM)	19 (6.4)	19 (6.4)	5 (7.4)	43 (6.5)

Other	5 (1.7)	7 (2.3)	0 (0.0)	12 (1.8)
Total Patients	298 (100.0)	298 (100.0)	68 (100.0)	664 (100.0)

The average weight and volume of resected margins by treatment group during the lumpectomy is presented in Table 21. The treatment groups appear to be similar with respect to weight and volume of resected margins.

Table 21 - Descriptive Statistics of Resected Margins Weight and Volume by Treatment Group

Specimen Parameter	Treatment Group						All	
	Device		Control		Roll-In Phase			
	n [a]	Mean (SD)	n [a]	Mean (SD)	n [a]	Mean (SD)	n [a]	Mean (SD)
Weight (g)	1000	6.6 (6.8)	329	7.5 (6.7)	219	6.0 (5.2)	1548	6.7 (6.6)
Volume (cm^3)	1044	7.9 (10.7)	344	9.1 (10.1)	252	7.4 (8.2)	1640	8.1 (10.2)

[a] Difference between weight and volume in number of margins is due to missing data.
Source: Statistical Table M-54 in Appendix 10.2.2.

F. Study Results

1. Safety Results

14 adverse events (AEs) were reported, all being categorized as serious adverse events (SAEs) per study protocol definition. One SAE was possibly related to the study device, a wound infection requiring hospitalization and treatment with antibiotics.

Table 22 - Frequency of Serious (All) Adverse Events by System Organ Class, Preferred Term, and Treatment Group

System Organ Class/Preferred Term		Treatment Group							
		Device N=298		Control N=298		Roll-In Phase N=68		Any N=664	
		N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients
Any	Any	6	6 (2)	5	5 (2)	3	3 (4)	14	14 (2)
Infections and infestations	Any	2	2 (1)	1	1 (0)	2	2 (3)	5	5 (1)
	Acute tonsillitis	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Breast abscess	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
	Cellulitis	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)
	Postoperative wound infection	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Urinary tract infection	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)
Injury, poisoning and procedural complications	Any	2	2 (1)	3	3 (1)	0	0 (0)	5	5 (1)
	Fractured sacrum	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Post procedural haemorrhage	0	0 (0)	2	2 (1)	0	0 (0)	2	2 (0)
	Procedural dizziness	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Procedural pain	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
	Uterine leiomyoma	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)
Reproductive system and breast disorders	Any	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
	Breast haematoma	0	0 (0)	1	1 (0)	0	0 (0)	1	1 (0)
Vascular disorders	Any	1	1 (0)	0	0 (0)	1	1 (1)	2	2 (0)
	Hypertension	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (0)

System Organ Class/Preferred Term		Treatment Group							
		Device N=298		Control N=298		Roll-In Phase N=68		Any N=664	
		N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients	N SAEs	N (%) Patients
	Hypertensive crisis	1	1 (0)	0	0 (0)	0	0 (0)	1	1 (0)

Adverse events associated with device malfunction or incorrect device readings causing incorrect surgeon action is both a safety and an effectiveness issue. Incorrect surgeon action is therefore further discussed in the Effectiveness Results section below. While an approximately 5 minute prolongation of the operative procedure associated with device use, this prolongation cannot be associated with specific patient adverse events. In addition, while damage to the tissue exposed to the MarginProbe device is a potential problem, an assessment for tissue damage was not considered to be feasible in the pivotal study. From the available data this issue has not been reported.

2. Effectiveness Results

Primary Effectiveness Endpoint: There were a total of 163 patients in the SOC+Device arm and a total of 147 patients in the SOC arm who were in the PSS dataset (i.e. with at least one positive margin by histology on the main specimen). The CSR primary effectiveness endpoint results are provided in Table 23.

The device failed to give a reading on 38 (2%) margins out of 1788 margins measured from 298 subjects. This did not impact the primary endpoint.

Table 23 - The CSR Primary Effectiveness Endpoint Results

Primary Endpoint	Dataset	SOC + Device	SOC	Difference (95% CI)	
CSR	PSS	71.8% (117/163)	22.4% (33/147)	49.3% (39.0%,58.7%)	p < 0.0001

Secondary Effectiveness Endpoint Results:

	Endpoint	Dataset	SOC + Device	SOC	p-value or CI
1º	CSR	PSS	71.8% (117/163)	22.4% (33/147)	p < 0.0001
2º	Incomplete Surgical Re-excision	AVS	15.4% (46/298)	38.3% (114/298)	p < 0.0001*

2º	Full Detection	PSS	62.6% (102/163)	NA	95% CI: 54.7% – 70%*
2º	Re-excision Procedure Rate	AVS	20.8% (82/298)	25.8% (94/298)	p = 0.3177*
2º	Positive Margin Presence	AVS	30.9% (92/298)	41.6% (124/298)	p = 0.0082*
2º	Total Tissue Volume Excised	NSS	92.7 cm3	69.9 cm3	p = 0.0031*

* Unadjusted analysis
PSS = cohort of patients that had a histologically cancer positive lumpectomy main specimen margin
NSS = cohort of patients that had all histologically negative lumpectomy main specimen margins
AVS = the entire cohort of patients (both the PSS and NSS cohorts together)

Table 24 - Secondary Effectiveness Endpoint Results

Secondary Endpoints	Dataset	SOC + Device	SOC	p-value or CI
Incomplete Surgical Re-excision	AVS	15.4% (46/298)	38.3% (114/298)	p < 0.0001*
Full Detection	PSS	62.6% (102/163)	NA	95% CI: 54.7% – 70%*
Re-excision Procedure Rate	AVS	20.8% (82/298)	25.8% (94/298)	p = 0.3177*
Positive Margin Presence	AVS	30.9% (92/298)	41.6% (124/298)	p = 0.0082*
TTV excised in the primary lumpectomy procedure (cm^3)	NSS	92.7 cm^3	69.9 cm^3	p = 0.0031*

* Unadjusted analysis

Of the endpoints listed, the clinically relevant endpoint of re-excision procedure rate showed a 5 percentage point reduction in the SOC+Device arm versus SOC arm.

The reoperation procedure rate is further described in Table 25. Note that fewer patients in the SOC+Device arm required a second operation (71 patients in the SOC+Device arm versus 85 patients in the SOC arm). Recall that the MarginProbe device was only used during the initial lumpectomy operation and not during reoperations. More patients in the SOC+Device arm versus the SOC were converted to mastectomy. There are numerous reasons for conversion to mastectomy and therefore this finding cannot be directly attributable to device use.

Table 25 - Re-excision (including conversion to mastectomy)

	Lumpectomy	**Additional Resections**			**Total**	**p-Value**
Procedure #	**1**	**2**	**3**	**4**		
SOC+Device	298	62	7	2	71 (23.8%)	0.3177
SOC	298	77	7	1	85 (28.5%)	

Conversion to mastectomy in device arm = 18/298
Conversion to mastectomy in control arm = 13/298 p = 0.46

The following additional analyses, Table 26 and Table 27, provide information regarding diagnostic performance of the device per margin and per patient (ignoring location).

Table 26 - Diagnostic Performance (per-margin)

	Sensitivity(%) (95% CI)‡	Specificity(%) (95% CI) ‡	PPV†(%) (95% CI) ‡	NPV†(%) (95% CI) ‡
SOC+Device	73.8 (68.1,79.4)	45.1 (41.8,48.3)	21.6(20.1,23.1)	89.4(87.2,91.4)
SOC	33.9 (27.5,40.5)	83.4 (81.1,85.7)	29.5(25.1,34.3)	86.0(84.8,87.2)
(SOC+Device)-SOC	39.9(31.4,48.1)	-38.3(-42.4, -34.5)	-7.9(-12.8, -3.4)	3.4 (1.0,5.7)
Device only††	75.2(69.3,80.5)	46.4 (42.6,49.9)	22.3 (20.7,23.8)	90.1 (88.0,92.1)
SOC	33.9 (27.5,40.5)	83.4 (81.1,85.7)	29.5(25.1,34.3)	86.0(84.8,87.2)

Device-SOC	41.3(33.0,49.5)	-37.0(-41.4, -33.0)	-7.2(-12.1,-2.6)	4.1(1.8,6.4)

†PPV and NPV calculated using Bayes theorem on sensitivity and specificity, assuming a common prevalence across the two study arms of 17.0%. ‡95% Bootstrap percentile intervals.
†† There were 38 margins with a missing device reading.(6 pathology positive margins and 32 pathology negative margins)

Table 27 - Diagnostic Performance per patient ignoring location

	Sensitivity(%) 95% CI	Specificity (%) 95% CI	PPV†(%) 95%CI	NPV†(%) 95% CI
SOC+Device	98.8(95.6,99.9)	5.9(2.6,11.3)	53.2(52.1,54.4)	81.9(49.0,95.4)
SOC	68.7(60.1,76.1)	53.6(45.4,61.8)	61.6(56.7,66.3)	61.3(54.4,67.7)
(SOC+Device)-SOC	30.1(22.6,38.2)	-47.7(-56.6, -38.3)	-8.4(-13.6, -3.5)‡	20.6(-9.2,42.0)‡
Device only	96.3(92.2,98.6)	8.9(4.7,15.0)	53.4(51.9,54.9)	68.9(46.2,85.2)
SOC	68.7(60.1,76.1)	53.6(45.4,61.8)	61.6(56.7,66.3)	61.3(54.4,67.7)
Device-SOC	27.6%(19.6,36.0)	-44.7% (-54.0, -34.9)	-8.2 (-13.5,-3.1)‡	7.6(-16.6,27.9)‡

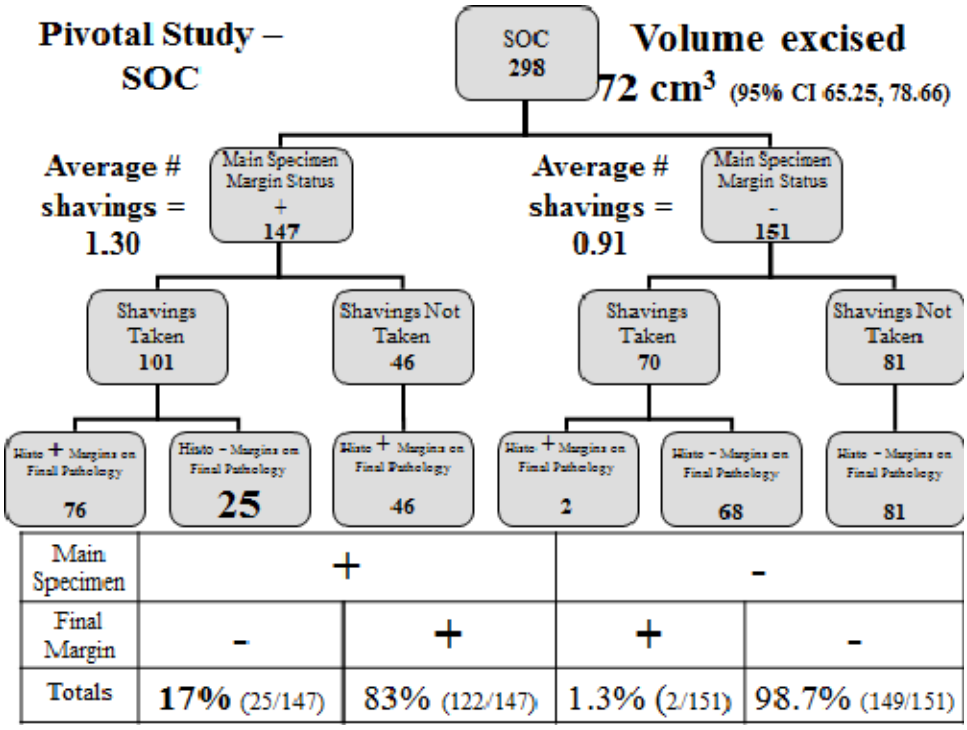
†PPV and NPV calculated using Bayes theorem assuming a common prevalence across the two study arms of 52%.
‡95% Bootstrap percentile intervals.

The Figures 12 and 13 provide a more comprehensive assessment of what occurred in each arm of pivotal study.

As shown in Figure 13, 298 SOC patients were enrolled. An average of 72 cm3 of tissue was excised during the initial lumpectomy. There were 147 patients with cancer positive main specimens and 151 cancer negative main specimens. Of the 147 cancer positive main specimens, 25 or 17% were converted to cancer negative final margins with cavity shavings.

In the SOC arm, shavings were not taken in 46+81 or 127/298 subjects.

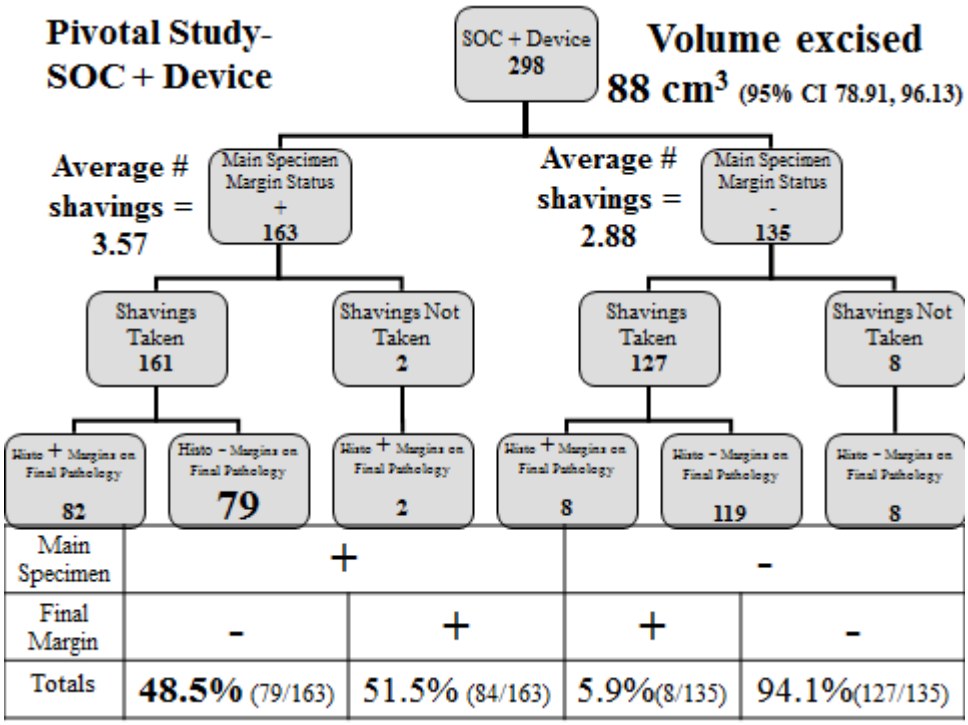
Figure 13 - Pivotal Study Patient Flow Chart - SOC Arm



As demonstrated in Figure 14, 298 patients were enrolled in the SOC+Device arm. An average of 88 cm3 of tissue was excised during the initial lumpectomy. There were 163 patients with cancer positive main specimens and 135 cancer negative main specimens. Of the 163 cancer positive main specimens, 79 or 49% were converted to cancer negative final margins with cavity shavings.

In the SOC+Device arm, shavings were not taken in 2+8 or 10/298 subjects.

Figure 14 - Pivotal Study Patient Flow Chart - SOC+Device Arm



XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Pivotal Study Additional Analyses

While not powered to detect differences across subpopulations, there was a trend for outside of US patient populations to experience greater clinically relevant benefit than for the US population of patients enrolled as shown in Table 28.

Table 28 - Pivotal Study Results across Subpopulations

		US Patients n = 98		Israel Patients n = 566	
Endpoint		SOC + Device	SOC	SOC + Device	SOC
1º	CSR	69.7%	22.4%	85.7%	22.7%
2º	Incomplete Surgical Re-excision	17.3%	38.8%	6.1%	35.4%
2º	Full Detection*	59.9%	N/A	81%	N/A

2º	Re-excision Procedure Rate	34.5%	48%	4.8%	22.7%
2º	Positive Margin Presence	53.5%	82.4%	38.1%	86.4%
2º	Total Tissue Volume Excised (cm^3)	92.4	82.6	97.6	95.9
Diagnostic Device Performance		SOC + Device	SOC	SOC + Device	SOC
Sensitivity (%) 95% CI†		73.4 (66.8,79.6)		87.8 (76.8,98.8)	
Specificity (%) 95% CI†		44.7% (40.8,48.8)		53.9% (46.0,62.0)	

*Full detection is for Device (not SOC+Device arm)
†95% Bootstrap percentile intervals.

B. Product Development Clinical Studies

Product development clinical studies were conducted at various stages of the product development process, as summarized in Table 29. None of these studies were pre-approved by FDA.

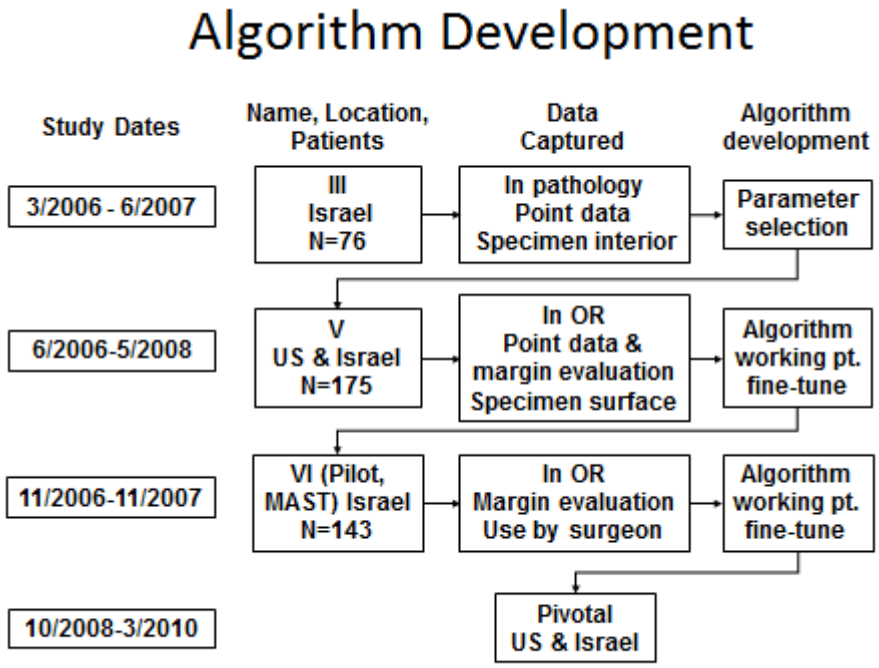
Table 29 - Developmental Clinical Studies of the MarginProbe

Study Number	Study Name	# Subjects	Product Description	Primary Objective	Principal Results
III	"Point-by-point" study in pathology - phase II 3/2006 – 6/2007	N=76	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Obtain database set and assess performance – phase II	Device use has no permanent effect on tissue (macroscopic or microscopic) Device performance per-point on bread-loafed lumpectomy specimens: sensitivity 100% and specificity 87% on homogeneous samples, sensitivity 70% and specificity 70% on full dataset
V	Intraoperative blinded study - phase II 6/2006 – 5/2008	N=175	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Assess intraoperative performance on the resection surface of lumpectomy specimens and evaluate adjunctive device contribution to SOC	Even with a limited point sampling by the device, per-patient detection rate is superior with Device+SOC (73%) as compared to SOC alone (46%)

MAST	Pilot Study 11/2006 – 11/2007	N=300	MarginProbe System Probe & MarginProbe System Type 1.0 system console	Assessment of device detection performance and clinical utility in a randomized, controlled (patient is blinded), intended use fashion. Assess cosmetic outcome associated with device use compared to SOC.	- Device is safe for intraoperative use - Re-excision rate is reduced by 56% (p=0.0027) - Positive margin identification guiding intraoperative resection is superior in Device+SOC arm (60%) compared to SOC (41%) - Cosmesis is not affected by device use - Excised tissue volume is not affected by device - Performance is the same for both palpable and non-palpable lesions

The product development study results were used to develop the MarginProbe System algorithm in the manner described in Figure 15.

Figure 15 - Algorithm Development Process.



1. **Study III**

Study III was conducted to create the classification database of actual tissue measurements using the MarginProbe paired with their histology at point level. For each point measured with the device the pathology was taken at that same point. Device measurements were performed at the interior of the lumpectomy specimen (following its sectioning at the pathology lab).

The specimens used for this study were taken from women with palpable tumors who had undergone lumpectomy or mastectomy. The study was performed in Israel at 4 study sites. The patient demographics and cancer specifics of the specimens used to create the classification dataset are summarized in Table 30. Table 31 illustrates the classification data set that was derived in Study III.

Table 30: Study III - Patient Demographics and Cancer Specifics

Sites	4 (Israel)
N	77 patients and 81 specimens (4 patients bilateral disease)
Mean Age (range)	62.64 years (36 - 85)
Mean Tumor Size (range)	1.65 cm (0.1 – 3.5)

Fine Needle Localization	33 specimens	
Sentinel Node Biopsy (Both Blue Dye & Radioisotope)	43 specimens	
Cancer Pathology	Infiltrating Ductal (IDC)	46
	DCIS	8
	Mixed	8
	Infiltrating Lobular (ILC)	6
	Other	3
	Not stated	4
Grade	I	3
	II	34
	III	20
HER2 positive	18	
Estrogen Positive	60	
Progesterone Positive	46	

Table 31: Study III - Classification Data Set

Number of tissue measurement data points	869
– Excluded data points	116
Valid data points	753
– Normal	588 (78%)
– Malignant	165 (22%)

The ROC curves of the device performance in Study III are shown in Figure 16. This figure includes three datasets: (1) tissues containing at least 75% of a single tissue type; (2) all tissues containing at least 50% of a single tissue type; and (3) the full

dataset collected in the experiment, containing cancers of all sizes (down to 0.15-mm-diameter features).

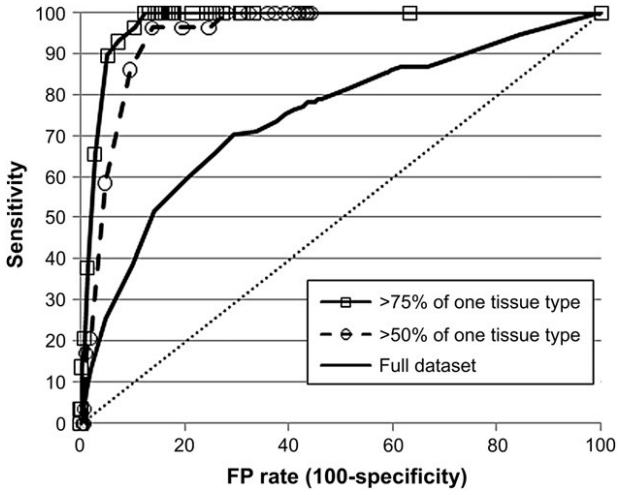


Figure 16 - Study III - ROC curves of 3 different datasets

When the composition of the tissue being measured by the probe (i.e. directly underneath the 7 mm footprint of the probe) was more homogeneous, there was greater sensitivity and specificity in MarginProbe™ readings as shown in Table 32.

Table 32 - Study III - Sensitivity and Specificity in MarginProbe™ Readings

Percentage single tissue type within probe's 7 mm diameter footprint	Specimen description	Device Performance
> 75% singe tissue type	22 cancerous, from 15 patients 425 nonmalignant	Sensitivity 1.00 (95% CI: 0.85–1) Specificity 0.87 (95% CI: 0.83–0.90)
≥ 50% single tissue type	29 cancerous, from 18 patients, and 567 nonmalignant	Sensitivity 1.00 (95% CI: 0.88–1) Specificity 0.72 (95% CI: 0.68–0.76).
Full dataset containing cancers of all sizes (down to 0.15-mm-diameter features)	165 cancerous sites from 50 patients, and 588 nonmalignant sites	Sensitivity 0.70 (95% CI: 0.63–0.77), Specificity 0.70 (95% CI: 0.67–0.74)

The performance for different histopathology types are also summarized in Table 33. [The two most common groups, invasive ductal carcinoma (IDC) and ductal

carcinoma in situ (DCIS), have sensitivities of 0.68 (95% CI: 57– 77) and 0.63 (95% CI:45–79), respectively]

Table 33: Study III - Device Sensitivity for Different Histopathology Subgroups

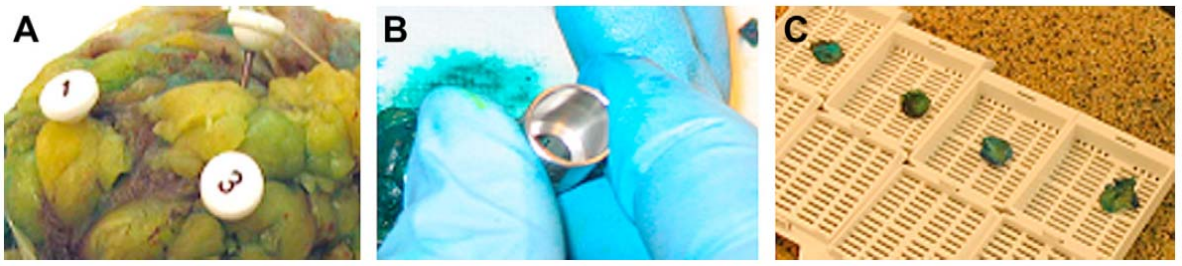
Cancer histopathology	Number of samples	Detected	Detection rate (95% CI)
Infiltrating Ductal Carcinoma (IDC)	87	59	0.68 95% CI:57– 77
Ductal Carcinoma in-situ (DCIS)	35	22	0.63 95% CI:45–79
Infiltrating Lobular Carcinoma (ILC)	7	5	0.71
IDC+ DCIS	25	21	0.84
ILC+ DCIS	3	3	1.00
Other	8	6	0.75
Full dataset	165	116	0.70

2. **Study V**

Study V was a blinded study with MarginProbe™ System Type 1.0 device to assess performance of the device on the cut surface tissue of lumpectomy specimens, as compared to histology.

Surgeons were blinded to the device outputs and could not act on device outputs. The device measurements (maximum of 20) were taken intraoperatively on the surface of fresh intact lumpectomy specimens. The orientation of each measurement site was noted. For each marked site, the corresponding 7 mm wide tissue specimen was processed *en-face* and microscopically evaluated as positive or negative for malignancy.

Figure 17 - Study V - Sampling Process

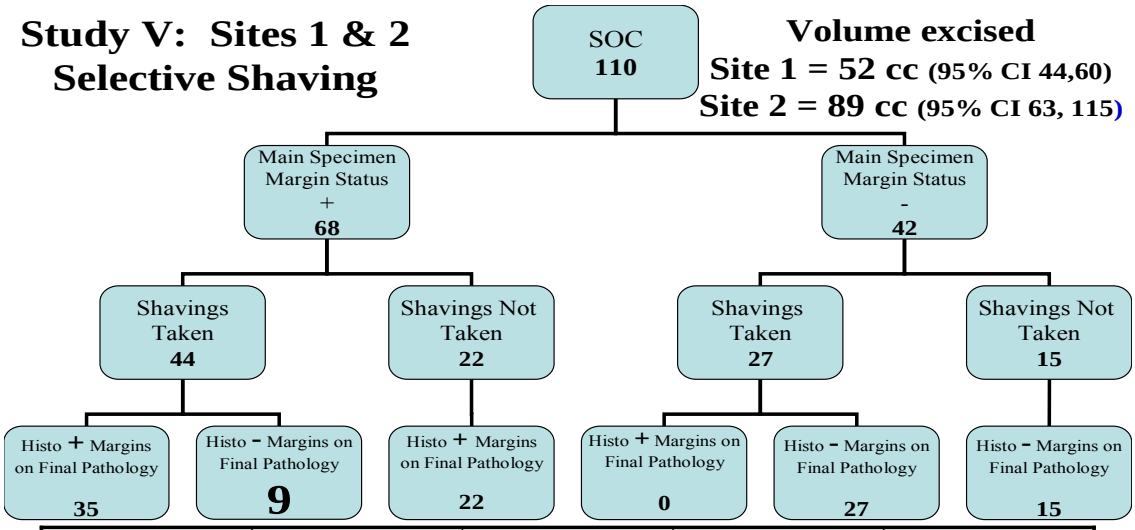


A total of 175 subjects were enrolled in 3 sites during this study. Surgeons at 2 institutions included in this study (site 1: US site, n=101 patients; site 2: OUS site, n=9 patients) excised additional margins only where deemed necessary ("selective" re-excision). Practice at the third institution (US site, n=65 patients, 66 specimens) was to routinely re-excise all margins from the cavity ("total" re-excision).

While results from Study V served to further inform the MarginProbe product development, Study V also serves to provide a comparison of differences in standard of care selective versus empiric total cavity shaving. Patients who receive empiric, routine re-excision of all margins have greater conversion of initial positive lumpectomy margins to final negative margins. The observed effect is illustrated below in Figures 18 and 19 comparing the final pathologies from patients treated at study sites 1 and 2 (selective re-excision) versus study site 3 (total re-excision).

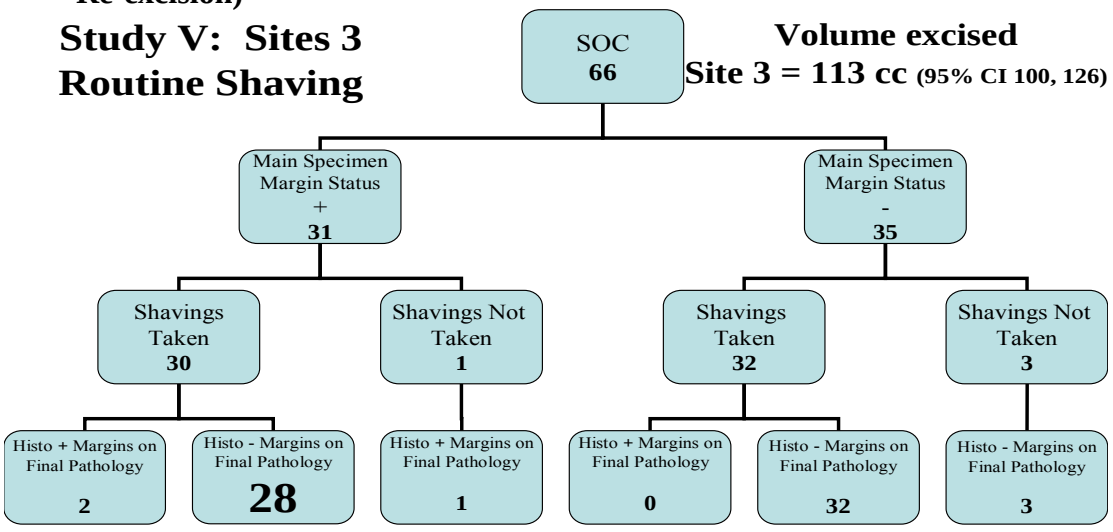
There is also literature (see references list below) suggesting that the standard, empiric practice of complete/partial lumpectomy cavity shavings in the same operative setting as the initial lumpectomy can reduce the incidence of incomplete cancer resection and produces greater volumes of tissue resection.

Figure 18 - Study V - Final Pathologies from Patients Treated at Study Sites 1 and 2 (Selective Re-excision)



Main Specimen	+	+	-	-
Final Margin	-	+	+	-
Totals	9/68	57/68	0/42	42/42

Figure 19 - Study V - Final Pathologies from Patients Treated at Study Site 3 (Total Re-excision)



Main Specimen	+	+	-	-
Final Margin	-	+	+	-
Totals	28/31	3/31	0/35	35/35

3. MAST Study

This MAST pilot study was performed in Israel. It was a prospective, randomized, controlled study designed to compared SOC lumpectomy with to SOC+Device lumpectomy. Three hundred subjects at 11 sites were enrolled (n=149 device arm; n=151 control arm).

The MAST study design was similar to the Pivotal study however there were some differences. The MAST study involved a different MarginProbe device algorithm, different device use instructions (i.e. surgeons used the device at their discretion with respect to extent of device use and tissue targeted and were not required to act on positive MarginProbe device readings), an assessment of post-lumpectomy breast symmetry using a 4 point scale, and intra-operative pathology as part of SOC--being used in approximately 20% of the cases.

The difference in protocols across studies may be reflected in the results of the SOC arm in the MAST Study compared to the pivotal IDE investigation. The results are provided in Figures 20 and 21 below.

Figure 20 - MAST Study - Final Pathologies - SOC Arm

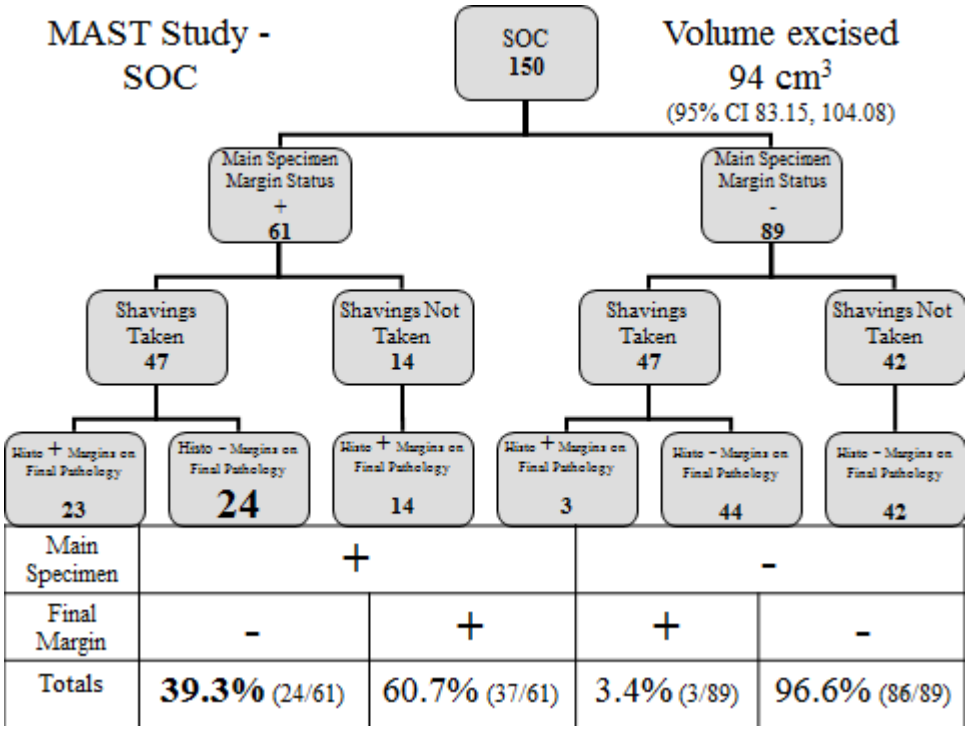
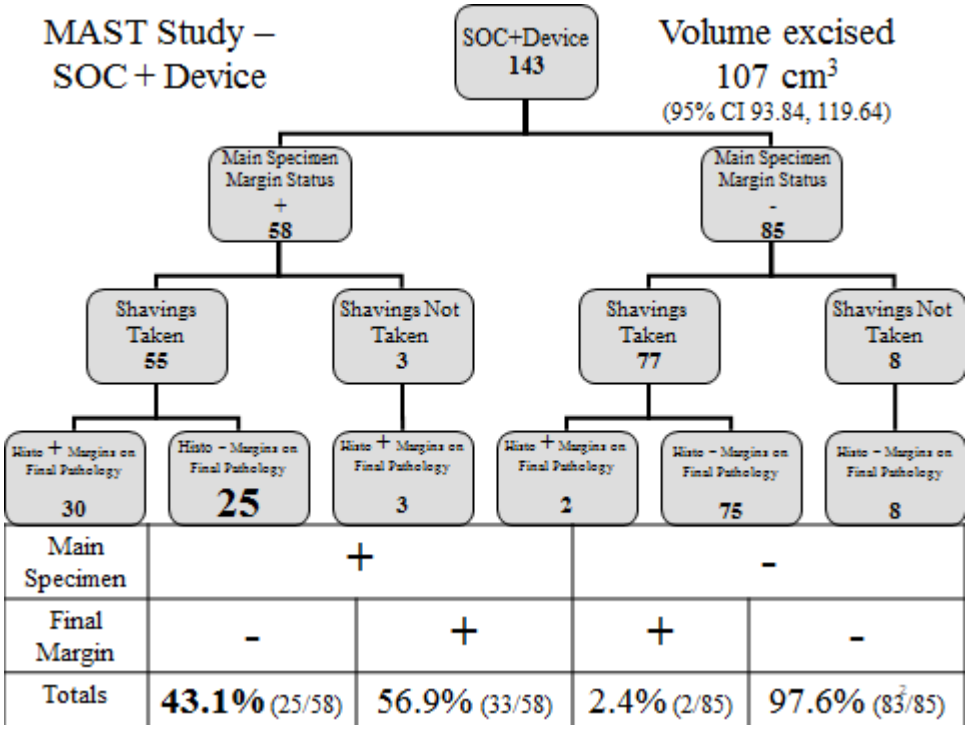


Figure 21 - MAST Study - Final Pathologies - SOC+Device Arm



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XII. PANEL MEETING RECOMMENDATION AND FDA'S POST_PANEL ACTION

Panel Meeting Recommendation

An advisory meeting was held on June 21, 2912, the General and Plastic Surgery Devices Panel discussed the data included in the Dune Medical Devices, Inc. PMA for the MarginProbe System.

- The Panel voted 11-0-0 (yes, no, abstain) that there is a reasonable assurance that the Dune Medical MarginProbe System is safe for use in patients who meet the criteria specified in the proposed indication.
- The Panel voted 8-1-2 (yes, no, abstain) that there is reasonable assurance that the Dune Medical MarginProbe System is effective for use in patients who meet the criteria specified in the proposed indication.
- The Panel voted 10-1-0 (yes, no, abstain) that the benefits of the Dune Medical MarginProbe System do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

A. Effectiveness Conclusions

The results from the pivotal clinical study indicate that the device when used as an adjunctive tool for identification of cancerous tissue at the margins (≤ 1mm) of the ex-vivo lumpectomy specimen following primary excision of breast cancer, there was a 5 percentage point reduction in re-operation. Device use was associated with an increase in tissue volume in the primary lumpectomy procedure (92.7 cm^3 vs. 69.9 cm^3).

Comparing the sensitivity and specificity of the Device and the Device + SOC versus the SOC per margin (not per specimen), the device had a sensitivity of 75.23% and a specificity of 46.38%; while the sensitivity of the SOC arm was 33.94% and specificity was 83.39%.

However, the study design contained bias favoring the study arm. The study design allowed for 3 opportunities to take lumpectomy cavity shavings in the study arm (SOC+Device) and 2 opportunities to take lumpectomy cavity shavings in the control arm (SOC). In addition, the reason for taking additional shavings of the lumpectomy cavity - whether a shaving was taken because of surgeon suspicion, ultrasound imaging, radiographic imaging, or a positive MarginProbe device reading - was not documented. This makes it difficult to determine whether the results observed were due to the MarginProbe device or confounding factors.

It is noted that standard, empiric complete lumpectomy cavity shavings in the same operative setting as the initial lumpectomy also can also reduce the incidence of incomplete cancer resection but can be associated with greater volumes of healthy tissue resection.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

14 adverse events (AEs) were reported, all being categorized as serious adverse events (SAEs) per study protocol definition. Only 1 SAE was possibly related to the study device, a wound infection requiring hospitalization and treatment with antibiotics.

The risk of reduced breast cosmesis due to false positive MarginProbe device readings and subsequent resection of greater volumes of healthy tissue was not assessed in the pivotal study and therefore its incidence and severity is unknown.

C. Benefit-Risk Conclusions

Due to the high rate of incomplete surgical resection of breast cancer at the time of lumpectomy, point of care diagnostics designed to reduce the incidence of retained cancer following initial lumpectomy are necessary.

It is currently estimated that approximately 30% of patients undergoing lumpectomy for breast cancer need to return to the operating room for re-lumpectomy due to incomplete surgical resection of the breast cancer at the time of the initial lumpectomy. Re-lumpectomy is associated with delays adjuvant breast cancer treatment. Re-lumpectomy due to retained cancer is also associated with greater tissue volume resection which may produce more severe breast disfigurement.

The relative contribution of the MarginProbe device was not assessed in the pivotal study since the reason for taking additional shavings of the lumpectomy cavity—whether a shaving was taken because of surgeon suspicion, ultrasound imaging, radiographic imaging, or a positive MarginProbe device reading--was not documented. It is therefore unclear whether the pivotal study results were due to specimen imaging, to greater time taken by the surgeon deliberately assessing each margin during the process of MarginProbe device use, or to the MarginProbe device readings.

Breast cosmesis was not assessed in the pivotal study. There was a greater volume of tissue removed in the study arm versus the control arm. The amount of additional volume of healthy tissue resected that produces a clinically relevant change in breast appearance is unknown and may not be the same volume across patients and among breast surgeons. It is therefore unclear whether the resection of greater volumes of healthy tissue associated with device use produces greater breast disfigurement or not.

Standard, empiric complete lumpectomy cavity shavings in the same operative setting as the initial lumpectomy also can reduce the incidence of incomplete cancer resection but also produces greater volumes of tissue resection (reference list below). For this reason routine cavity shaving is routine practice for only 10% of surgeons (Blair 2009).

This finding was demonstrated in the sponsor's early clinical work with the MarginProbe device at Study Site 3 of Study V. Study Site 3 surgeons routinely performed complete lumpectomy cavity shavings immediately following the lumpectomy in the same operative setting. The conversion rates of initially positive main lumpectomy margins to final negative outermost margins are shown in the table below. Note that there was a conversion rate of positive main specimen margins to negative final margins for ~90% at Study Site 3 patients where full cavity shavings were performed. In comparison, Study Sites 1 and 2 performed selective lumpectomy cavity shavings at surgeon discretion. Table 34 below also includes the pivotal study results for comparison purposes.

Table 34 - Margin Status of Lumpectomy Specimens and Final Margins

Lumpectomy margin = LM Final margin = FM		Margin status of lumpectomy specimen (LM) and final margins (FM)			
		LM +	LM +	LM -	LM -
		FM -	FM +	FM -	FM +
Pivotal Study	SOC (n = 298) mean volume excised = **71.95 cm³** (95% CI: 65.25-78.66)	25/147 (17%)	122/147 (83.0%)	149/151 (98.7%)	2/151 (1.3%)
	SOC + Device (n = 298) mean volume excised = **87.52 cm³** (95%CI: 78.91-96.13)	79/163 (48.5%)	84/163 (51.5%)	127/135 (94.1%)	8/135 (5.9%)
Study V No MarginProbe Input	Site 1 SOC (n = 100) *Selective* **52 cm³** (95%CI: 44-60)	9/61 (14.8%)	52/61 (85.2%)	40/40 (100%)	0/40 (0%)
	Site 2 SOC (n = 9) *Selective* **89 cm³** (95%CI: 63-115)	0/7 (0%)	7/7 (100%)	2/2 (100%)	0/2 (0%)
	Site 3 SOC* (n=65) *Full* **113 cm³** (95%CI: 100-126)	28/31 (90.3%)	3/31 (9.7%)	35/35 (100%)	0/35 (0%)

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The study design together with missing information regarding the reason and timing for taking additional lumpectomy cavity shavings makes it difficult to determine whether the results observed were due to the MarginProbe device or confounding factors. However, there was a reduced reoperation rate in the study arm versus the control arm in the pivotal study. Therefore:

- For surgeons who do not perform empiric lumpectomy cavity shavings of all margins in the same operative setting as the initial lumpectomy, the probable benefits outweigh the probable risks.

- For surgeons who do perform empiric lumpectomy cavity shavings of all margins in the same operative setting as the initial lumpectomy, the available data is not sufficient to determine whether or not the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With a 5 percentage point reduction of reoperation rate in the study arm versus the control arm in the pivotal study, the probable benefits outweigh the probable risks for surgeons who do not perform empiric lumpectomy cavity shavings of all margins in the same operative setting as the initial lumpectomy.

XIV. CDRH DECISION

CDRH issued an approval order on December 27, 2012

The applicant must conduct a post-approval study as described below:

MarginProbe System U.S. Post-Market Study: This study will be conducted as per agreement dated December 20, 2012 (teleconference/email). The purpose of the study is to determine the MarginProbe's diagnostic accuracy at the margin level and impact on the Positive Margin Presence originating from the main specimen after the first lumpectomy surgery. These questions will be addressed in a prospective, multicenter, randomized, double arm study. A total of 440 newly enrolled patients treated in a total of 10-20 centers in the United States. The study participants will be followed for 6 months. The co-primary effectiveness endpoint include 1) diagnostic accuracy (sensitivity and specificity) at the margin level with a pre-specified clinically meaningful minimum margin level sensitivity and specificity 2) Positive Margin Presence originating from the main specimen after the first lumpectomy surgery. The secondary endpoints include the rate of additional operations (re-excision and re-operation), cosmesis, positive margin presence on the outermost shaving after the first lumpectomy surgery and diagnostic accuracy at the patient level. For safety, all adverse events will be monitored until the patient's follow-up for the study is completed.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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