DILON TECHNOLOGIES

MARGINPROBE®

(MarginProbe System – Model AC0300001)

Sterile Disposable Probe

Instructions for Use

Instructions for use P/N: PB0501051

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PATENTS

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TRADEMARKS

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Indications for Use

The 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.

Device Description

The MARGINPROBE® System is a medical device 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.
- The probe is a detachable, sterile, single-use, single-patient component with a 3-year shelf life. It is connected to the console by two RF cables and a vacuum tube, via a single connector.

The MARGINPROBE® System is used in patients undergoing breast surgery as an adjunct to standard methods of margin assessment. It is used on excised tissue immediately following excision (i.e., within 20 minutes) to measure the dielectric properties of the tissue and to characterize it as malignant (positive) or normal (negative). Expected duration of intraoperative device use is 5 minutes.

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 a wide range of RF frequencies. The RF energy is confined to the vicinity of the probe tip. The energy level per measurement is less than 0.2 mJ with a power lower than 0.3 mW. The maximum field voltage is 1V p-p.

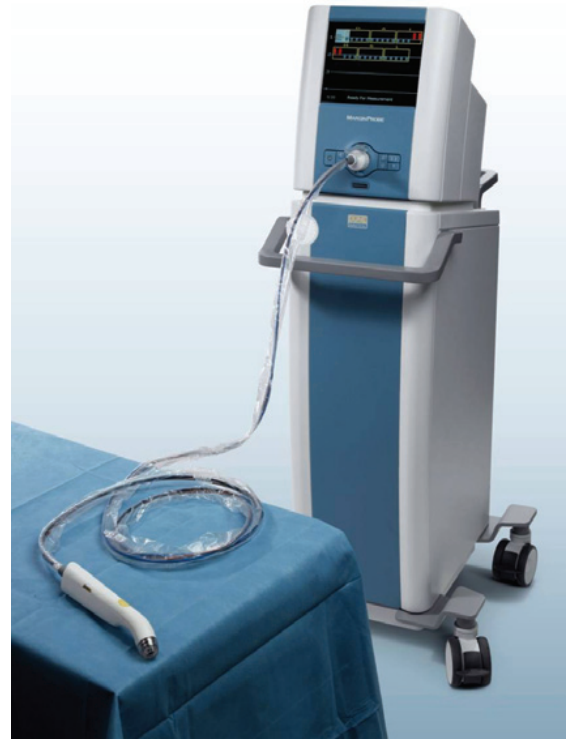


Figure 1. MarginProbe® System

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 during measurement. The device uses a classification algorithm that was created using breast cancer tissue samples.
The sensor creates an electromagnetic field which exponentially decays in the tissue. 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 the MARGINPROBE® device assessed lumpectomy tissue readings at the surface margins ≤ 1 mm in depth.
The MARGINPROBE® System Probe should be used to sample the entire surface of the specimen, taking approximately 5-8 measurements per margin surface, and up to 12 points per face for larger specimens. Measurements should be performed at both evenly spaced intervals and suspicious sites. Readings are displayed on the MARGINPROBE® System Console as either positive or negative.
If any one of the device readings is positive, the margin should be considered positive, and an appropriate surgical action should be taken.

Contraindications

The 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

Warnings

- The MARGINPROBE® should be used on tissue specimens within 20 minutes of excision.
- The MARGINPROBE® should not be used in patients who undergo full cavity excision following removal of the main lumpectomy specimen during the initial lumpectomy procedure.
- The MARGINPROBE® has not been studied in patients with:

- Multicentric disease (histologically diagnosed cancer in two different quadrants of the breast), unless resected in a single specimen
- Bilateral disease (diagnosed cancer in both breasts)
- Neoadjuvant systemic therapy
- Previous radiation in the operated breast
- Prior surgery at the same site in breast
- Implants in the operated breast
- Pregnancy
- Lactation
- Cryo-assisted localization

Precautions

- The main ex-vivo lumpectomy specimen is defined as the initially excised lumpectomy specimen, without any of the lumpectomy cavity shavings that may have been subsequently taken during the procedure. The device has not been studied for use on tissue shavings excised from the lumpectomy cavity.
- The MARGINPROBE® System should be used in addition to standard intraoperative methods of assessing margin status.
- Moving the probe before suction release may potentially damage and affect tissue histopathology.
- The MARGINPROBE® Probe should only be used with the MARGINPROBE® Console.
- The MARGINPROBE® Probe is designed for single patient, single-use only and must be properly discarded after use.
- The MARGINPROBE® Probe is supplied sterile. If the sterile pack is torn or has been opened, do not use the probe.
- Do not use a MARGINPROBE® Probe that has passed its expiration date.

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 the next section (Clinical Data) below.

Clinical Data

MarginProbe Post Approval Study

The MarginProbe Post Approval Study was conducted to confirm the study results observed in the pivotal IDE clinical trial of MarginProbe. The study was mandated as part of the PMA approval and the PAS protocol was approved under PMA P110014 S001. A subsequent amendment was approved under PMA P110014 S010 to allow for remote follow up. The results of this Post Approval Study demonstrated consistency with the Pivotal Study results and confirms product performance in a study that is consistent with the "real world" usage.

A summary of the clinical study is presented below.

Summary of the Post-Approval Study Methods

A. Study Objective

The study objective was to enhance the body of clinical evidence beyond the pivotal IDE study. Specifically, the PAS was designed to determine the MarginProbe System's diagnostic accuracy at the Margin Level and impact on Positive Margin[1] presence originating from the Main ex-vivo lumpectomy specimen after the initial lumpectomy surgery.

B. Study Design

This was a prospective, multicenter, randomized, double arm, controlled study of adjunctive use of the MarginProbe System (SOC + Device) vs. Standard of Care, including additional inspection (SOC + Additional Inspection).

The surgeon performed a lumpectomy to obtain the main specimen, which potentially contained the diagnosed lesion. All main specimens were suture oriented, so as to uniquely define the aspects of the specimen relative to the body (lateral, medial, superior, inferior, deep, anterior). The orienting suture was placed in the center of the margin as indicated by the surgeon. The surgeon visually inspected and palpated the tissue and margins were resected if deemed necessary.

Randomization took place immediately after the main specimen was excised, oriented, center marked, palpated, and palpation-based margins resected, if necessary. In the Device arm, MarginProbe was used on the six margins of the specimen. According to device readings, margins were resected, as necessary. Intra-operative imaging was performed following device use.

Pathological assessment was standardized and identical for both study arms. Pathologists were blinded to the randomization assignment when they evaluated each sample. Subjects were followed until the end of the lumpectomy procedure. Data were collected up until six (±1) months after the lumpectomy.

In the event that re-excision (lumpectomy/mastectomy) was required during the data collection period, the data collection period was

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

reinitiated according to the above outline. Data were collected on any additional ipsilateral surgical procedures, including axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). The study flow chart is presented in Figure 2 below.

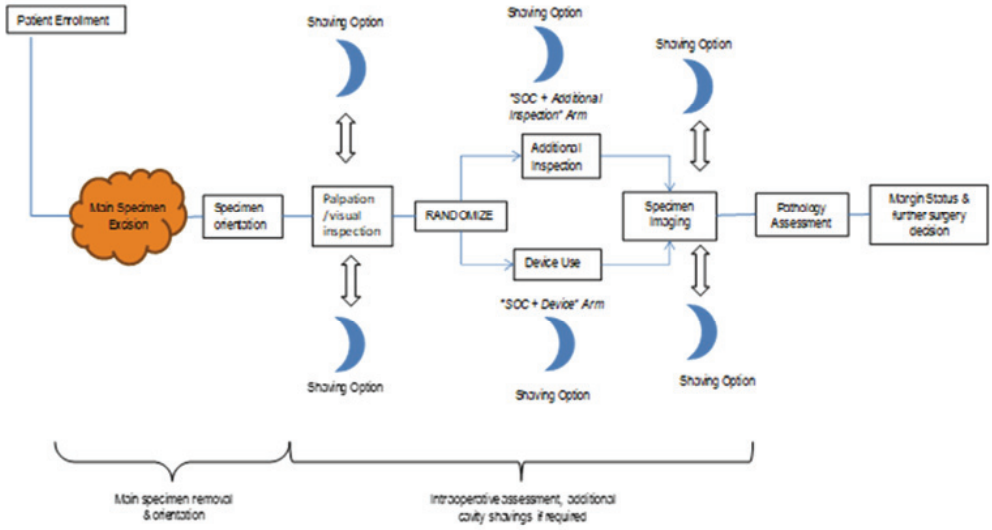


Figure 2: PAS Study Design

C. Study Population

The study was a multi-center study randomizing 440 subjects (recruited 438), 220 in each arm (recruited 214 subjects in the SOC + Device arm and 224 subjects SOC + Additional Inspection arm). The study was designed to include a maximum of 20 centers within the United States (U.S.), with at least half of them being new centers that did not enroll subjects in the pivotal IDE study. A total of eleven centers were utilized in the study and a summary of each center with their enrollment is provided in section F.

1. Eligibility Criteria

Enrollment in the Post Approval Study was limited to patients who met the following inclusion criteria:

1) Women histologically diagnosed with carcinoma of the breast.
2) Women with non-palpable malignant lesions, requiring image guided localization.
3) Undergoing lumpectomy (partial mastectomy) procedure.
4) Age 18 years or more.
5) Signed ICF.

Patients were not permitted to enroll in the Post Approval Study if they met any of the following exclusion criteria:

1) Multi-centric disease (histologically diagnosed cancer in two different quadrants of the breast).
2) Bilateral disease (diagnosed cancer in both breasts).
3) Neo-adjuvant systemic therapy.
4) Previous radiation in the operated breast.
5) Prior surgery in the same site in the breast.
6) Woman histologically diagnosed by an open biopsy procedure.
7) Implants in the operated breast.
8) Pregnancy.
9) Lactation.
10) Participating in any other investigational study for either drug or device which could influence collection of valid data under this study.
11) Subjects for whom complete cavity shaving is planned (sites where this is the routine practice of the investigator will also be excluded from participation in the study).

2. **Disposition of Patients:**

Table 1 presents the disposition for the 470 subjects screened for participation in the study. Of the 470 subjects screened, 25 did not meet inclusion/exclusion criteria. Of the 445 subjects who met inclusion/exclusion criteria, 7 declined participation: 2 subjects chose to have surgery at a different facility, 2 withdrew consent, 1 declined due to logistical issues, 1 due to COVID-19 medical center restrictions prohibiting clinical study enrollment and 1 due to study suspension by IRB. The balance of enrolled subjects was 438 which is in line with the target sample size.

Table 1: Subject Disposition

	N [%]
Subjects screened	470 (100.0%)
Subjects that did not meet the inclusion/ exclusion criteria	25 (5.32%)
Subjects that met the inclusion/ exclusion criteria	445 (94.68%)
Subjects for whom participation declined	7 (01.49%)
Total subjects enrolled	438 (93.19%)

3. Demographic and Other Baseline Characteristics

presents demographic data by treatment group. The study population was women with a mean age of 63. There were no apparent differences in demographic characteristics between treatment groups. The study population reflects the United States breast cancer population in age at diagnosis, as well as incidence by race and ethnicity.[27] In fact, as opposed to many clinical studies wherein the minority population is underrepresented, this clinical study included a higher percentage of minority women with African Americans comprising nearly 18% of the study population.

Table 2: Demographic Data by Treatment Group

Parameter	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
N (%)	214 (48.86%)	224 (51.14%)	438 (100.0%)	
Age (yrs) Mean (S.D.)	62.17 (10.79)	63.29 (10.71)	62.74 (10.75)	-1.13 (-3.15, 0.89)
Female n (%)	214 (100.00%)	224 (100.00%)	438 (100.00%)	
African American	34 (15.89%)	44 (19.64%)	78 (17.81%)	-3.75% (-10.90% - 3.39%)
American Indian or Alaska native	0 (00.00%)	1 (00.45%)	1 (00.23%)	-0.44% (-1.31% 0.43%)
Asian	8 (03.74%)	6 (02.68%)	14 (03.20%)	1.06% (2.24% 4.37%)
Other, Mixed	1 (00.47%)	1 (00.45%)	2 (00.46%)	0.02% (-1.24% 1.28%)
White	142(66.36%)	148 (66.07%)	290 (66.21%)	0.28% (-8.58% 9.14%)
White-Hispanic	20 (09.35%)	14 (06.25%)	34 (07.76%)	3.09% (-1.93% 8.12%)
Not known	09 (04.21%)	10 (04.46%)	19 h(04.34%)	-0.26% (-5.2% 4.76%)

Table 3 presents baseline characteristics by treatment group. There were no apparent differences in baseline characteristics between treatment groups. The study population reflects the average BMI of 29.6 for women in the United States.[28] The BRACA categorization for the women in the study was largely unknown at the time of enrollment which is consistent with clinical practice. This was also largely unknown in the PMA pivotal

clinical study as well as BRACA testing is commonly not performed until after lobectomy is performed.

Table 3: BMI, BRCA and Bra Cap Size

Parameter	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
BMI - mean (std)	29.68 (7.13)	29.39 (6.48)	29.53 (6.80)	-0.29 (-1.56, 0.99)
BRCA				
Yes	3 (01.40%)	2 (00.89%)	5 (01.14%)	0.51% (-1.49%, 2.51%)
No	49 (22.90%)	37 (16.52%)	86 (19.63%)	6.38% (-1.06%, 13.82%)
Not Known	162 (75.70%)	185 (82.59%)	347 (79.22%)	-6.89% (-14.48%, 0.71%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	
Bra Cup Size n (%) Subjects				
A	6 (02.80%)	4 (01.79%)	10 (02.28%)	1.02% (-1.79%, 3.83%)
B	35 (16.36%)	30 (13.39%)	65 (14.84%)	2.96% (-3.70%, 9.63%)
C	51 (23.83%)	54 (24.11%)	105 (23.97%)	-0.28% (-8.27%, 7.72%)
D	28 (13.08%)	36 (16.07%)	64 (14.61%)	-2.99% (-9.59%, 3.61%)
DD	16 (07.48%)	19 (08.48%)	35 (07.99%)	-1.01% (-6.08%, 4.07%)
DDD	2 (00.93%)	6 (02.68%)	8 (01.83%)	-1.74% (-4.22%, 0.73%)
E	1 (00.47%)	1 (00.45%)	2 (00.46%)	0.02% (-1.24%, 1.28%)
F	1 (00.47%)	0 (00.00%)	1 (00.23%)	0.47% (-0.45%, 1.38%)
G	0 (00.00%)	2 (00.89%)	2 (00.46%)	-0.89% (-2.12%, 0.34%)
Not known	74 (34.58%)	72 (32.14%)	146 (33.33%)	2.44% (-6.40%, 11.27%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	

Table 4 presents pre-operative diagnosis by treatment group. Table 4 presents the number of subjects with a diagnosis, with specific categories combined. For subjects with IDC + ILC, the Mixed Invasive category was used, and for subjects with invasive and non-invasive diagnoses, the Mixed

category was used. The Device and Control groups were similar with respect to diagnosis. The study population is largely consistent with the PMA pivotal study demographics albeit not exactly the same and is consistent with expectations in clinical practice in the US.

Table 4: Frequency Distribution of Subject Diagnosis (Combined Categories)

Subject Diagnosis	Treatment Group		All	Difference in proportions (Device + SOC – SOC + Additional Inspection), 95% CI
	Device + SOC	SOC + Additional Inspection		
Invasive Ductal Carcinoma	95 (44.39%)	99 (44.20%)	194 (44.29%)	0.20% (-9.11%, 9.50%)
Invasive Lobular Carcinoma	12 (05.61%)	17 (07.59%)	29 (06.62%)	-1.98% (-6.62%, 2.66%)
Ductal Carcinoma in Situ	47 (21.96%)	49 (21.88%)	96 (21.92%)	0.09% (-7.66%, 7.84%)
Tubular Carcinoma	1 (00.47%)	0 (00.00%)	1 (00.23%)	0.47% (-0.45%, 1.38%)
Mucinous Carcinoma	3 (1.40%)	0 (00.00%)	3 (00.68%)	1.40% (-0.17%, 2.98%)
Medullary Carcinoma	0 (00.00%)	0 (00.00%)	0 (00.00%)	0.00% (0.00%, 0.00%)
Papillary Carcinoma	2 (00.93%)	1 (00.45%)	3 (00.68%)	0.49% (-1.07%, 2.05%)
Other	7 (03.27%)	9 (04.02%)	16 (03.65%)	-0.75% (-4.25%, 2.76%)
Mixed [b]	45 (21.03%)	45 (20.09%)	90 (20.55%)	0.94% (-6.63%, 8.51%)
Mixed Invasive [a]	2 (00.93%)	4 (01.79%)	6 (01.37%)	-0.85% (-3.01%, 1.31%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)	

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

4. Surgical Procedure

Table 5 presents the number and percent of subjects with a palpable tumor excised during lumpectomy. While all subjects had non-palpable lesions at screening (inclusion criteria), the lesion may or may not have been palpable in the specimen after removal. There

were no apparent differences between treatment groups with respect to palpable tumors during excision.

Table 5: Frequency Distribution of Palpable Tumor during Lumpectomy by Treatment Group

Was the Tumor Palpable in The Excised Specimen	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
No	117 (54.67%)	110 (49.11%)	227 (51.83%)
Yes	97 (45.33%)	114 (50.89%)	211 (48.17%)
Total	214 (100.00%)	224 (100.00%)	438 (100.00%)

5. Pathology

Main specimen

Table 6 presents the volume of the main specimen. There were no apparent differences between treatment groups with respect to weight and volume of the main specimen.

Table 6: Descriptive Statistics of Specimen Volume by Treatment Group

Specimen Parameter	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
Mean (Std) Volume (cm^3)	50.19 (78.35)	46.58 (55.68)	48.34 (67.63)

Table 7 presents tumor type (as assessed by post-operative histopathology) by treatment group.

In Table 7, tumor type is presented as recorded in the CRF, and each subject could have more than one tumor type.

Table 7: Frequency Distribution for Tumor Type by Treatment Group

Subject Diagnosis	Treatment Group		All
	Device + SOC	SOC + Additional Inspection	
Invasive Ductal Carcinoma	141 (42.73%)	147 (41.76%)	288 (42.23%)
Invasive Lobular Carcinoma	18 (05.45%)	25 (07.10%)	43 (06.30%)

Ductal Carcinoma in Situ	143 (43.33%)	151 (42.90%)	294 (43.11%)
Tubular Carcinoma	4 (01.21%)	2 (00.57%)	6 (00.88%)
Mucinous Carcinoma	6 (01.82%)	7 (01.99%)	13 (01.91%)
Medullary Carcinoma	1 (00.30%)	0 (00.00%)	1 (00.15%)
Papillary Carcinoma	0 (00.00%)	2 (00.57%)	2 (00.29%)
No tumor found	10 (03.03%)	12 (03.41%)	22 (03.23%)
Other	7 (02.12%)	6 (01.70%)	13 (01.91%)
Total	330 (100.00%)	352 (100.00%)	682 (100.00%)

6. Resected Margins

presents average volume of resected margins by treatment group during the lumpectomy. It appears that there is a trend toward a slightly higher volume in the Device group however, this difference is not statistically significant.

Table 8: Descriptive Statistics of Resected Margins Volume per Subject by Treatment Group

Specimen Parameter	Treatment Group				All	
	Device + SOC		SOC + Additional Inspection			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Volume (cm^3)	214	16.17 (19.83)	224	9.03 (15.66)	438	12.52 (18.16)

Note: The overall number of shavings is 660 for the SOC + Device arm and 361 for the SOC + additional inspection arm.

7. Specimen Management

Table 9 presents margin width in the operated breast after lumpectomy and re-excision procedures. The dimension of the excised sample is consistent between Device and Control groups.

Table 9: Margin Width in the Operated Breast after Lumpectomy and Re-Excision Procedures

	Device + SOC			SOC + Additional Inspection		
	Lumpectomy	Re-excision Procedure		Lumpectomy	Re-excision Procedure	
	N (%)			N (%)		
	1	2	3	1	2	3

>1 mm	163 (76.17%)	23 (67.65%)	1 (100.00%)	142 (63.39%)	22 (78.57%)	2 (100.00%)
<1 mm	51 (23.83%)	11 (32.35%)	0 (00.00%)	82 (36.61%)	6 (21.43%)	0 (00.00%)
All	214 (100.00%)	34 (100.00%)	1 (100.00%)	224 (100.00%)	28 (100.00%)	2 (100.00%)

D. Data Source

1. Data Sets analyzed:

All 438 women were included in the Safety analysis set.

The Efficacy Analysis was performed using data from all subjects that were randomized to either Device or Control, had valid histology data and had valid MarginProbe data (when assigned the Device Group). This analysis data set was termed All Valid Subjects, AVS. The AVS analysis set is consistent with the Safety data set and includes all 438 randomized subjects (214 Device and 224 Control). This was the data set utilized to analyze the Secondary Endpoint II.

For the Primary Endpoint, the analysis data set was based upon the Device performance and therefore included all Positive Specimen Subjects (PSS). A total of 214 subjects were included in this analysis data set. Further, the Secondary Endpoint (I) required an evaluation of Negative Specimen Subjects (NSS) and included 224 subjects in total. There were no subjects excluded from the Efficacy Analyses.

Table 10:Data Sets Analyzed - Number of Patients

Analysis Set	Subjects Included	Treatment Group		All N (%)
		Device + SOC N (%)	SOC + Additional Inspection N (%)	
Safety Set	All subjects for whom surgical procedure was initiated	214 (100.00%)	224 (100.00%)	438 (100.00%)
Effectiveness Sets				
AVS (SE II[a])	All randomized subjects	214 (100.00%)	224 (100.00%)	438 (100.0%[b])
PSS (PE[a])	Positive Specimen	89 (41.59%)	125 (55.80%)	214 (48.86%)
NSS (SE I[a])	Negative Specimen	122 (57.01%)	102 (45.54%)	224 (51.14%)

[a] Corresponding name of analysis set from the Main SAP.

[b] Represents the percent of all subjects included in effectiveness analyses.

E. Key Study Endpoints

1. Co-primary effectiveness endpoints:

1) Sensitivity at the Margin Level
2) Specificity at the Margin Level
3) Incomplete Surgical Resection (ISR[2]) - Positive Margin on the Main ex-vivo lumpectomy specimen after the initial lumpectomy surgery that was not addressed by taking a shaving(s) corresponding to the positive margin(s).

2. Secondary effectiveness endpoints:

1) Proportion of subjects with Positive Margin presence on the Outermost Shaving after the initial lumpectomy surgery (PMO[3])
2) Cosmesis evaluation:
   - Objective evaluation by an evaluator blinded to arm assignment.
   - Subject's self-reported evaluation.
3) Repeat lumpectomy rate - Proportion of subjects who underwent a repeat lumpectomy procedure.
4) Repeat lumpectomy and mastectomy rate - Proportion of subjects who underwent a repeat lumpectomy procedure or a mastectomy.
5) Diagnostic Accuracy at the Subject Level (ignoring location) - Proportion of subjects from whom shavings were taken.

3. Safety Endpoint:

The safety endpoints in this study were Adverse Events (AE's) and Serious Adverse Events (SAE's).

F. Total number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of eleven (11) centers were utilized in the study and a summary of each center with their enrollment and follow up rate are provided in Table 11 below.

[2] ISR is a focused assessment of what is within the control of the MarginProbe device and that is to cause additional cavity shavings. The pathology of the shavings is outside of the scope of this endpoint.
[3] PMO is a clinically relevant endpoint that considers the pathology of the shavings.

Table 11: Number and Percentage of Subjects' Randomization to Each Center, and Overall, by Treatment Group

Site #	Site Name	Treatment Group			Follow-up Rate	
		Device + SOC	SOC + Additional Inspection	All	VISIT 2 All	*VISIT 3 All
		N (%)	N (%)	N (%)	N (%)	N (%)
1	Pinnacle	18 (45)	22 (55)	40 (100)	40 (100)	39 (98)
2	Summit	09 (47)	10 (53)	19 (100)	19 (100)	16 (84)
3	Moffitt	38 (50)	38 (50)	76 (100)	76 (100)	41 (54)
4	Johns Hopkins	40 (50)	40 (50)	80 (100)	80 (100)	35 (44)
5	Rush	25 (49)	26 (50)	51 (100)	51 (100)	48 (94)
6	New Mexico	17 (48)	18 (51)	35 (100)	35 (100)	33 (94)
7	Northshore	20 (50)	20 (50)	40 (100)	40 (100)	39 (98)
8	Montefiore	21 (47)	24 (53)	45 (100)	45 (100)	40 (89)
9	Baptist	19 (48)	21 (52)	40 (100)	40 (100)	39 (98)
11	Sibley	06 (60)	04 (40)	10 (100)	10 (100)	6 (60)
12	Suburban	01 (50)	1 (50)	2 (100)	02 (100)	2 (100)
	Total	**214 (49)**	**224 (51)**	**438 (100)**	**438 (100)**	**338 (77)**

***Relevant to Secondary Cosmesis Endpoints only.**

G. Study visits and length of follow-up

1. Visit 1: Screening Visit

Eligibility was determined during the screening visit. Eligible subjects signed an informed consent form and a HIPPA release as part of the enrollment process.

2. Visit 2: Procedure Visit

Main Specimen

The main specimen (the initially excised lumpectomy specimen which potentially contained the diagnosed lesion) was excised using the surgeon's routine surgical technique. The main specimen was suture oriented, to uniquely define the aspects of the specimen relative to the body (lateral, medial, superior, inferior, deep, anterior). The orienting sutures were placed in the center of the margin, as identified by the surgeon. The surgeon visually inspected, palpated the tissue and related resection of margins was performed based on their assessment, if deemed necessary.

Randomization

Randomization took place immediately after the main specimen had been excised, oriented, center marked, palpated, and additional palpation-based resections performed. Specimen imaging (by ultrasound or radiography) was performed after randomization and device use (Device + SOC arm) or additional inspection (SOC + AI arm) was done.

Use of MarginProbe

For subjects in the device arm (Device + SOC), the MarginProbe was applied to the main specimen, at multiple locations on all specimen margins. The specimen surface was considered to have 6 margins: Medial, Lateral, Inferior, Superior, Anterior and Deep: each margin with its center marked by the surgeon. The device was applied to all 6 margins sequentially. The surface area of every margin of the main specimen was sampled, around and relative to the center marking. Additionally, the MarginProbe was applied to any areas not sampled that were suspicious by palpation and/or visual inspection. Device output was displayed to the user in real-time. Any device positive margin with one or more positive device readings was resected from the lumpectomy cavity. Positive margins not resected required a documented reason for the absence of resection. All excised tissues were submitted for routine permanent histopathology.

Blinding/Masking

For subjects in the Device + SOC (MarginProbe) arm, the device was used by the surgeon, while for subjects in the DOC+ Additional Inspection (Control) arm the device was not used. Consequently, participating surgeons were not able to be masked to the treatment. To

reduce any potential surgical bias, each subject was randomized after the main specimen was excised and additional palpation-based resections were performed. In this way the surgeon was not aware of the outcome until after specimen excision; whether or not s/he would have MarginProbe as an adjunct for positive margin detection.

Pathology

Pathological assessment was identical for both study arms. Pathologists were blinded to subject (specimen) allocation. Surgeons coordinated with pathologists to ensure that orientation conventions were agreed upon and that pathologists' interpretation of margin boundaries (medial, lateral, inferior, superior, anterior, and deep) were consistent with the surgeons. Margin depth, d, was to be noted in increments of 0.5 mm up to 2 mm, and in increments of 1 mm in the range 2-10 mm. Dimensions were to be noted for all specimens (main ex-vivo lumpectomy specimen and shavings). For the purpose of defining endpoints, a positive margin was defined as a margin microscopically measured and reported in the histopathology report to have cancer within 1 mm or less of the inked surface.

3. Visit 3: Follow- Up Visit

Subjects were followed until the end of surgical treatment.

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:

- Six (± one) months after the surgery date
- Conversion of the subject to mastectomy
- Latest ipsilateral repeat lumpectomy procedure

In the event that a re-excision (lumpectomy or mastectomy) procedure was performed during the data collection period, the data collection period was repeated according to the above outline. Data were collected on any repeated ipsilateral procedure, including ALND and SLNB. The end of data collection marked the study completion for each individual subject.

Summary of the Post-Approval Study Results

H. Final safety findings (key endpoints)

A total of sixteen (16) Serious Adverse Events were reported in the Post Approval Study (see Table 12 below):

Table 12: Serious Adverse Events by Severity and Treatment Group According to Patients

Severity	Treatment Group		
	Device+SOC N=214	SOC+ Additional Inspection N=224	Total N=438
Mild	2 (0.93%)	0 (0.00%)	2 (0.46%)
Moderate	1 (0.47%)	6 (2.68%)	7 (1.60%)
Severe	3 (1.40%)	4 (1.79%)	7 (1.60%)
Total	6 (2.80%)	10 (4.46%)	16 (3.65%)

A total of 190 AEs (not including SAEs) were reported in study, 98 (51.6%) within the Device+SOC group and 92 (48.4%) within the SOC+ Additional Inspection group. For 90 subjects AEs were reported, 48 (53.3%) subjects within the Device+SOC group and 42 (46.7%). From the 98 AEs within the Device+SOC group, 97 were classified as unrelated to the device and 1 was classified as possible related to the device. 2 deaths occurred during this study:1 death, at the Device+SOC group and 1 death at the SOC+ Additional Inspection group. The death at the Device+SOC group was classified as unrelated elated to the device. **Use of the MarginProbe device was safe and was not associated with increased risk over Control.**

I. Final effectiveness findings (key endpoints)

1. Co-primary effectiveness endpoints:

Success was demonstrated for all 3 co-primary endpoints, therefore meeting study objectives. The results confirm the ability of the device to assist in positive margin detection, reducing the presence of positive margins at the end of the lumpectomy by 45.45%.

- Sensitivity at Margin Level is 70.2%.
- Specificity at Margin Level is 48.7% for best case and 47.6% for worst case.

The Sensitivity and Specificity at Margin Level co-primary endpoints were met at 70.2% and between 47.6% (worst case) and 48.7% (best case) respectively. These results, comparable to the 73.8% sensitivity and 45.1% specificity reported in the MarginProbe Pivotal trial, confirm the device's consistent, predictable, and reliable ability to detect microscopic residual disease at the surface of the lumpectomy specimen.

- Incomplete Surgical Resection (ISR) rate

(Device+SOC=17.29%, SOC+Additional Inspection=31.70%, P=0.00056).

The device showed superiority over control in detection and immediate resection of all positive margins on the main specimen, thereby mitigating the primary risk of lumpectomy: Incomplete Surgical Resection (ISR) of cancer from the breast. ISR was significantly lower in the device arm compared to the control arm which was standard of care with additional inspection (17.29% vs. 31.7%, P=0.00056). These results again confirm and validate findings from the MarginProbe Pivotal Trial, which reported ISR as 15.4% and 38.3% for device and control respectively. (P<0.0001)

2. **Secondary effectiveness endpoints:**

Table 13 below presents the Secondary endpoints. The PMO endpoint met the established success criteria. The other secondary endpoints were all trending in the positive direction however, they did not achieve statistical significance primarily due to missing data or limited data size.

Endpoint	Description	Data set	Results	Conclusion
Positive Margin Presence on the Outermost Shaving after the Initial Lumpectomy Surgery (PMO)	1 = At least one positive margin on final pathology after first lumpectomy 0 = No positive margins on final pathology after first lumpectomy	All subjects	SOC + Device: With PMO/Without PMO(Rate) 51/163(23.83%) SOC + Additional inspection: With PMO/Without PMO(Rate) 83/141(37.05%)	PMO rate is statistically significantly improved in the SOC + Device arm
Cosmesis blinded evaluation	1 = Objective cosmesis evaluation is Excellent/Good 0 = Objective cosmesis evaluation is Fair/Poor The SOC+Device rate is compared to the SOC+Additional Inspection, using 10% non-inferiority margin.	Only subjects with cosmesis evaluation All subjects, best case scenario for the SOC+Device arm. Subjects with missing evaluation, counted as success. Subjects with missing evaluation, counted as failure. All subjects, worst case scenario for the SOC+Device arm.	SOC + Device: Excellent/Good vs. Fair/Poor (Rate) 85/78(52.15%) 136/78(63.55%) 136/78(63.55%) 85/129 (39.72%) 85/129 (39.72%) SOC + Additional inspection: Excellent/Good vs. Fair/Poor (Rate) 96/68(58.54%) 96/128(42.86%) 156/68(69.64%) 96/128 (42.86%) 156/68(69.64%)	Cases 1,3,4,5 The cosmesis blinded evaluation rate is not statistically significantly non-inferior in the SOC+Device arm. Case 2 The cosmesis blinded evaluation rate is statistically significantly non-inferior in the SOC+Device arm.
Repeat lumpectomy rate	1 = At least one Repeat Lumpectomy procedure 0 = No Repeat Lumpectomy procedure	All subjects, excluding subjects with a mastectomy second surgery	SOC + Device: With repeat lumpectomy/Without repeat lumpectomy (Rate) 17/193(8.10%) SOC + Additional inspection: With repeat lumpectomy/Without repeat lumpectomy (Rate) 24/192(11.11%)	Repeat lumpectomy rate is not statistically significantly improved in the SOC + Device arm
Repeat lumpectomy or mastectomy rate	1= At least one Repeat Lumpectomy or	All subjects, excluding 3 subjects with negative	SOC + Device: With repeat lumpectomy or	Repeat lumpectomy or mastectomy rate is not

Endpoint	Description	Data set	Results	Conclusion
	Mastectomy procedure 0 = No Repeat Lumpectomy or Mastectomy procedure	margins referred to a mastectomy reoperation.	mastectomy /Without repeat lumpectomy or mastectomy (Rate) 17/193(8.96%) SOC + Additional inspection: With repeat lumpectomy or mastectomy /Without repeat lumpectomy or mastectomy (Rate) 24/192(13.90%)	statistically significantly improved in the SOC + Device arm
Diagnostic accuracy at the subject level: Sensitivity at the subject level	Subjects are scored dichotomously: 1 (TP) = If at least one margin was shaved 0 (FN) = If no margins were shaved	Subjects with at least one histologically positive margin (margin£1 [mm]) on the main ex-vivo lumpectomy specimen.	SOC + Device: True positives/False negatives (Rate) 52/37(58.4%) SOC + Additional inspection: True positives/False negatives (Rate) 51/71(41.8%)	The Sensitivity at the subject level is statistically significantly improved in the SOC + Device arm
Diagnostic accuracy at the subject level: Specificity at the subject level	Subjects are scored dichotomously: 1 (TN) = If no margins were shaved 0 (FP) = If at least one margin was shaved The SOC+Device rate is compared to the SOC+Additional Inspection, using 52% non-inferiority margin.	All subjects with no histologically positive margins (margin>1 [mm]) on the main ex-vivo lumpectomy specimen	SOC + Device: True negatives/False positives (Rate) 8/117(6.4%) SOC + Additional inspection: True negatives/False positives (Rate) 39/63(38.23%)	The Specificity at the subject level is statistically significantly non-inferior in the SOC+Device arm.
Cosmesis self-reported evaluation	1 = Objective cosmesis evaluation is No difference/Slight difference 0 = Objective cosmesis evaluation is Moderate difference/Large difference	All subjects with at least one self-evaluated characteristic and in addition have completed the 6-month follow-up visit (in window)	SOC + Device: No difference/Slight difference vs. Moderate difference/Large difference (Rate) 113/16(87.60%) SOC + Additional inspection:	The cosmesis self-reported evaluation rate in the SOC+Device arm is statistically significantly non-inferior to the

Endpoint	Description	Data set	Results	Conclusion
	the SOC+Device rate is compared to the SOC+Additional Inspection rate, using 10% non-inferiority margin. The self-evaluation score is the average over 8 characteristics: Breast size Breast texture Nipple appearance Breast shape Breast elevation Scar tissue Fit to bra Fit to clothing		No difference/Slight difference vs. Moderate difference/Large difference (Rate) 133/11(92.40%)	SOC+Additional Inspection arm.

J. Study Strengths and Weaknesses

Table 14 summarizes the strengths and weaknesses of the of the Post Approval Study

Table 14: Strengths and weaknesses of the Post Approval Study

Strengths	Weaknesses
The actual incremental contribution of the MarginProbe device to a higher number of cavity shavings can be determined because the reason for taking a cavity shaving - i.e. SOC (clinical suspicion, or imaging) versus a positive MarginProbe reading - was documented.	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 decrease in ISR in the SOC+Device arm.
ISR, primary endpoint - reflects a specimen assessment which does not give any credit to intraoperative re-excision when only some of the positive margins on the main specimen are detected. This shows the actual potential of the technology to assist in real usage and not only in controlled environment.	ISR 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.
	ISR 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.
	Questionable clinical relevance in the time of "no tumor on ink" for IDC. This is addressed by the secondary endpoint of re-excision rate.

MarginProbe Pivotal Study

A clinical pivotal study was performed 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 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 3 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).

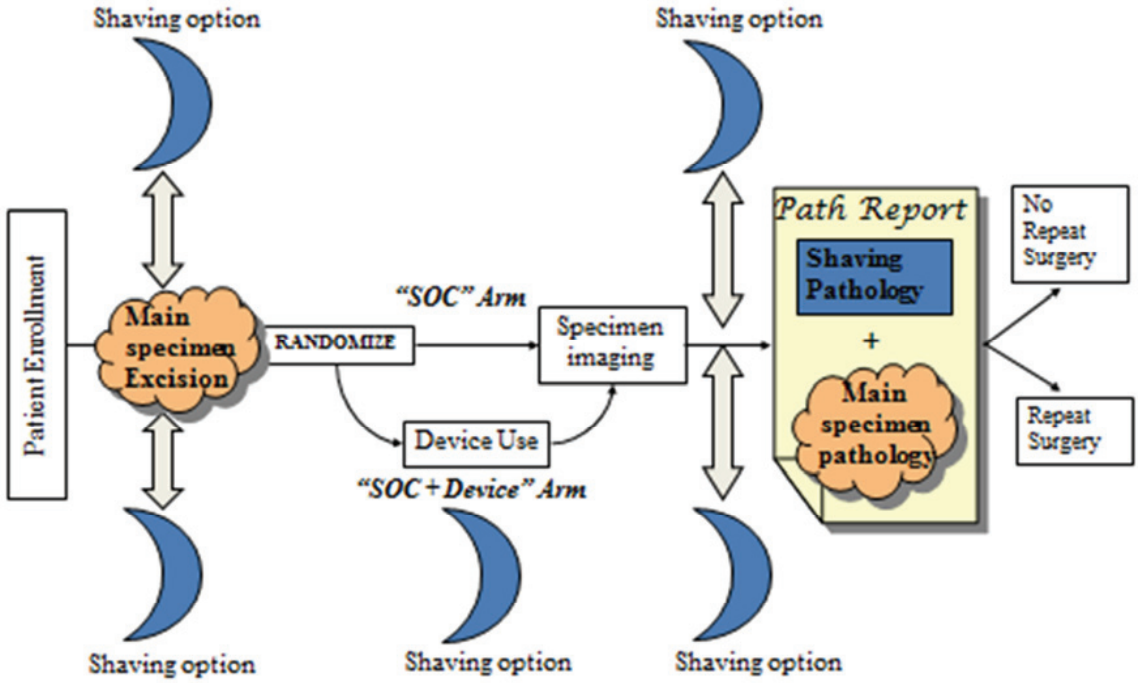


Figure 3 - Pivotal Study Design

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 4.

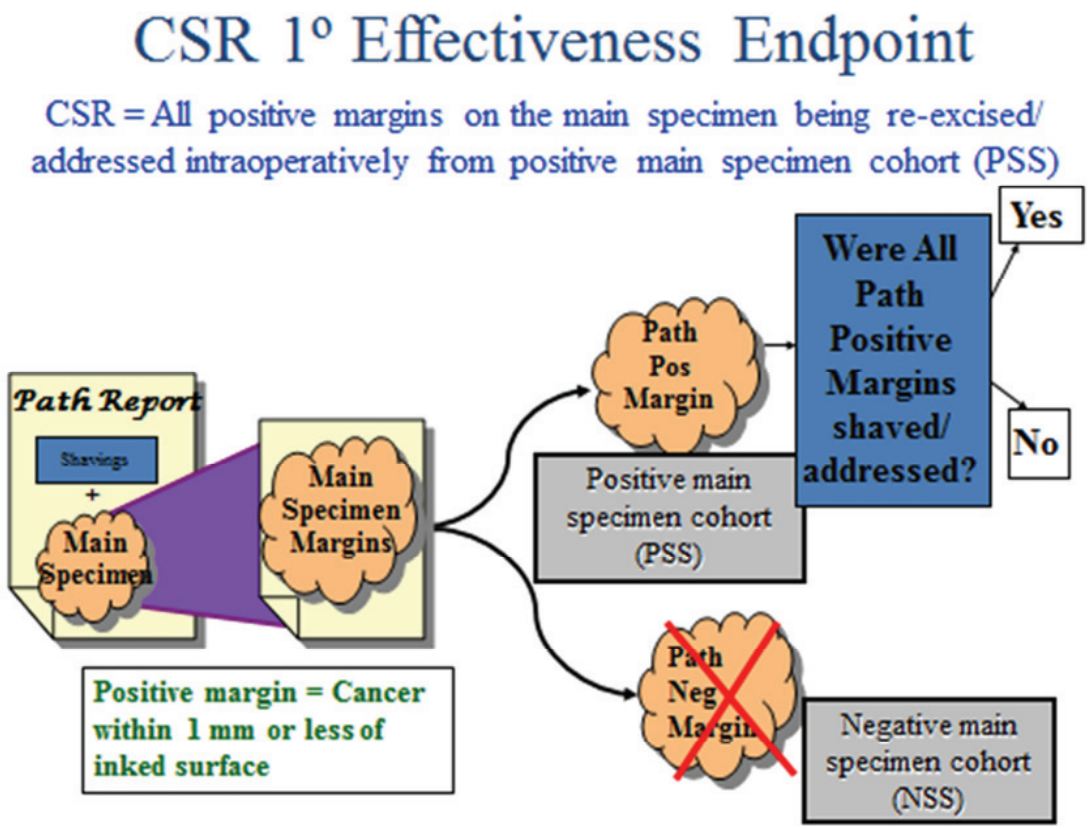


Figure 4 - Illustration of CSR Primary Endpoint

Figure 5 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.

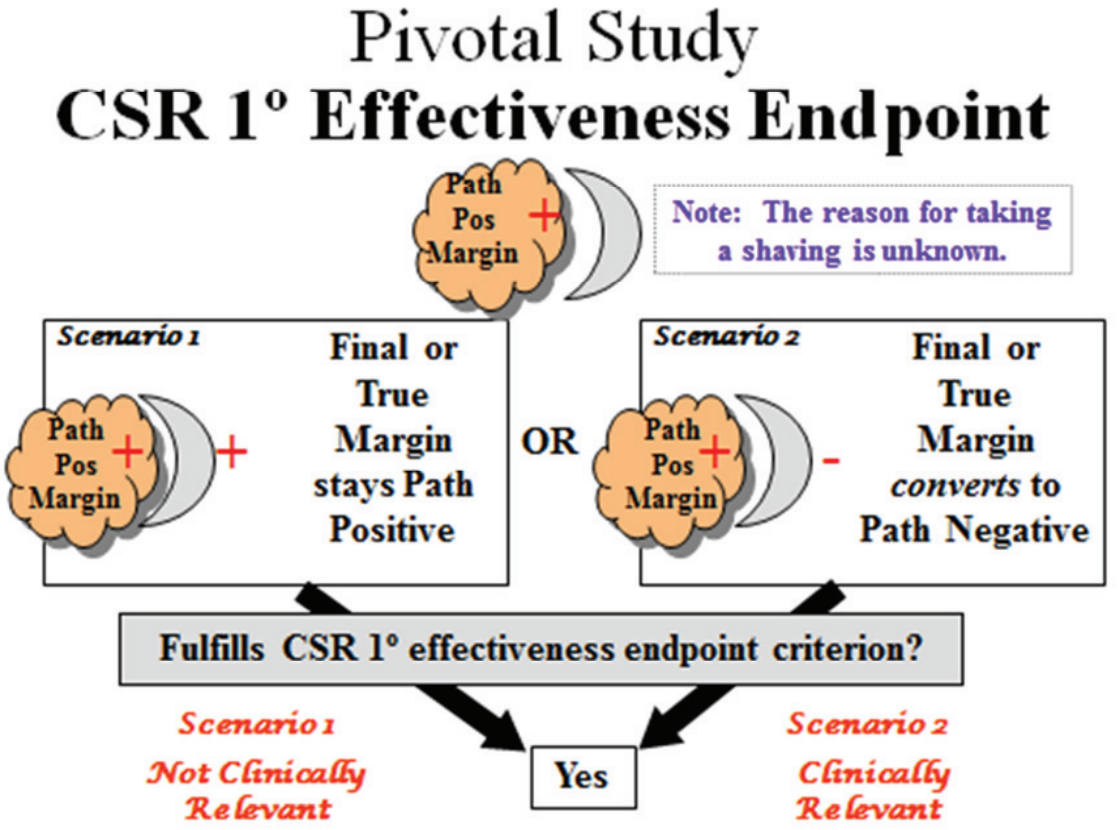


Figure 5 - CSR and Clinical Relevance

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

Table 15 - 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 16 below.

Table 16 - 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 17.

Table 17 - 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 18 and 19.

Table 18 - 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 19 - 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 primary lumpectomy procedure (cm3)	NSS analysis set Compared the groups using a 2-sided Wilcoxon Rank-Sum Test.	Total amount of tissue excised 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 20.

Table 20 - 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 21.

Table 21 - 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 22 and 23.

Table 22 - Demographics by Treatment Group

		Treatment Group	
Parameter	**Roll-In N=68**	**Device N=298**	**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 23 - Baseline Characteristics by Treatment Group

		Treatment Group	
Parameter	**Roll-In N=68**	**Device N=298**	**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)
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 24 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 24 - 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 Invasive[a]	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)
Mixed[b]	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 25 below. The majority of patients were diagnosed with stage II breast cancer and below.

Table 25 - 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 26. There were 84 subjects in device and control arms, and 19 in the roll-in subjects, for which HER2 status was not preformed.

Table 26 - 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 27 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 27 - 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 28 describes number of patients undergoing SLNB with dye or radioisotope or both.

Table 28 - 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 29 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 29 - 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 30. 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 30 - 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 31. The treatment groups appear to be similar with respect to weight and volume of resected margins.

Table 31 - 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 32 - 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)
	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 33.

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 33 - 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**

Table 34 - 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 cm3	69.9 cm3	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 35. 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 35 - Reoperation Procedure Rate 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 36 and Table 37, provide information regarding diagnostic performance of the device per margin and per patient (ignoring location).

Table 36 - 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)

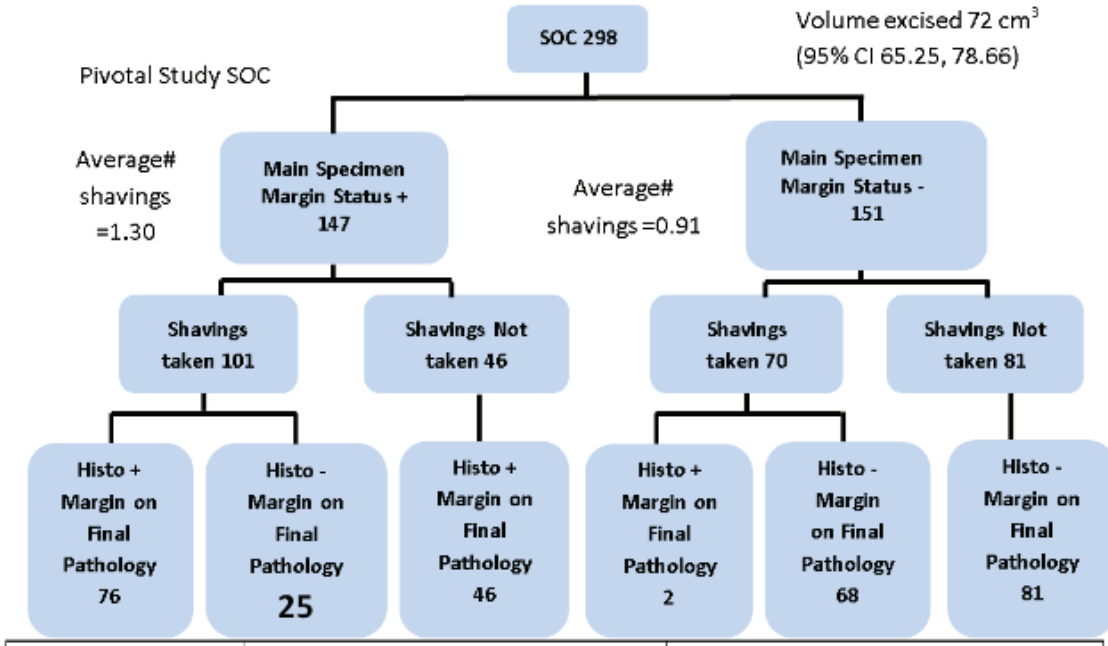
Table 37 - Diagnostic Performance per patient ignoring location

	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 6 and 7 provide a more comprehensive assessment of what occurred in each arm of pivotal study.
As shown in Figure 6, 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.

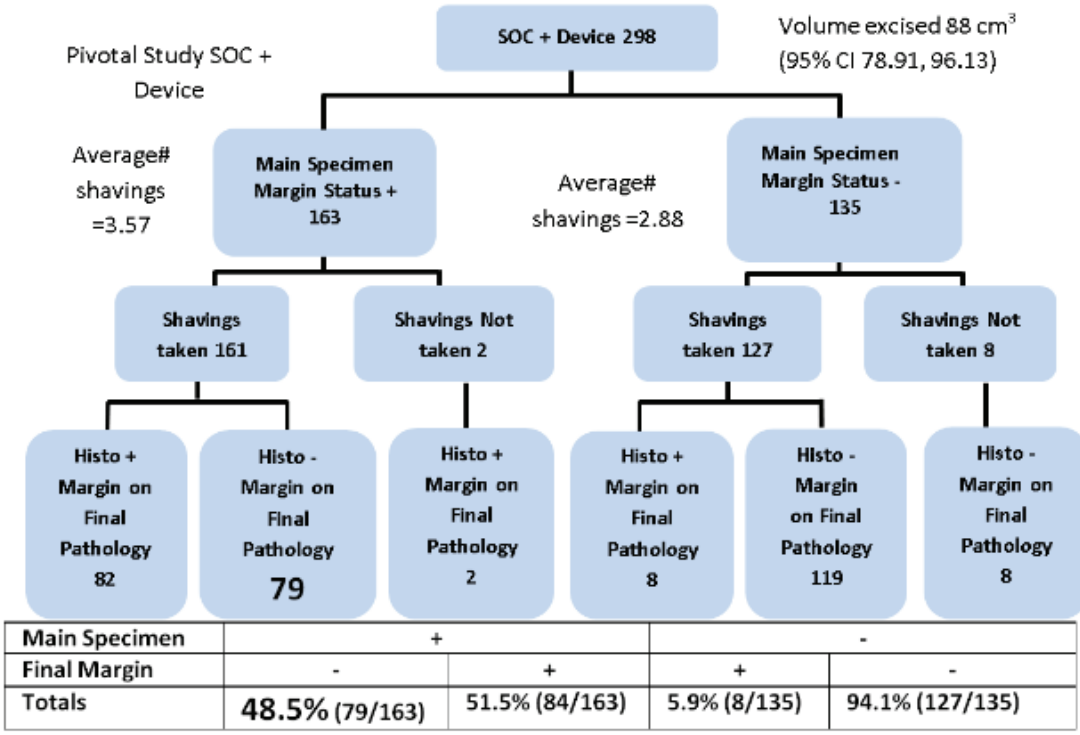


Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	17% (25/147)	83% (122/147)	1.3% (2/151)	98.7% (149/151)

Figure 6 - Pivotal Study Patient Flow Chart - SOC Arm

As demonstrated in Figure 7, 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.



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	48.5% (79/163)	51.5% (84/163)	5.9% (8/135)	94.1% (127/135)

Figure 7 - Pivotal Study Patient Flow Chart - SOC+Device Arm

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 38.

Table 38 - Pivotal Study Results across Subpopulations

		US Patients n = 566		Israel Patients n = 98	
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 39. None of these studies were pre-approved by FDA.

Table 39 - Summary of Developmental Clinical Studies

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 8.

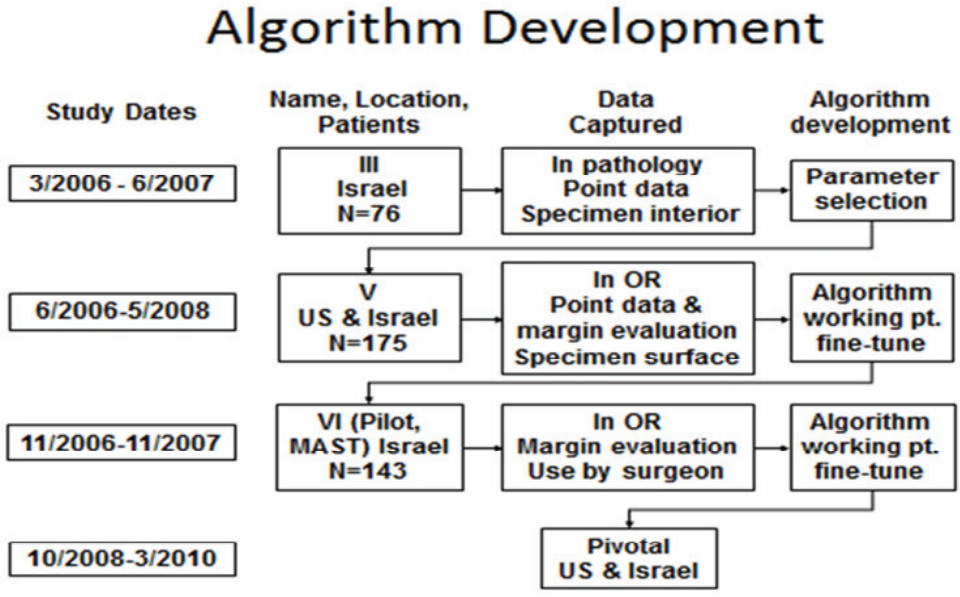


Figure 8 - Algorithm Development Process.

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 40. Table 41 illustrates the classification data set that was derived in Study III.

Table 40: 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 41: 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 9. 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).

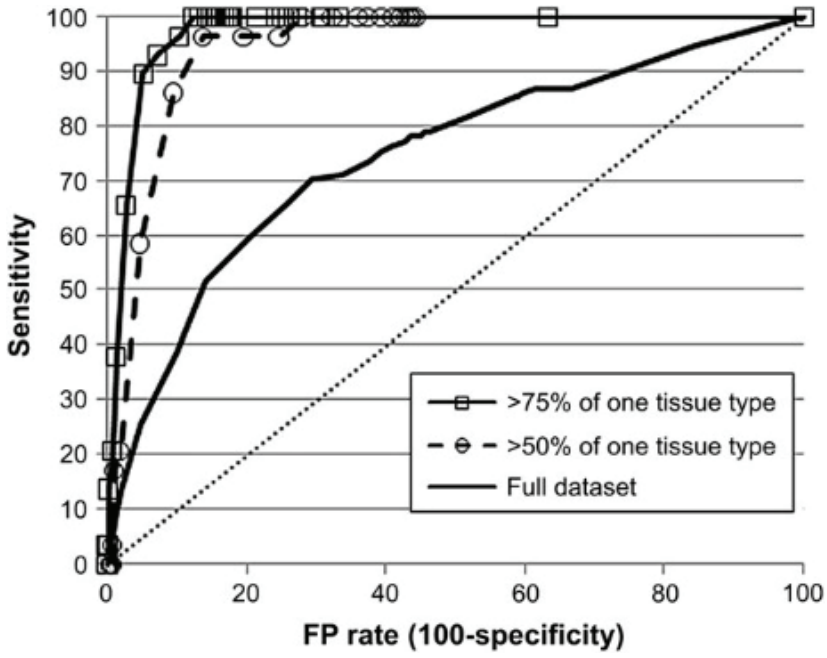


Figure 9 - Study III - ROC curves of 3 different datasets

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 42.

Table 42 - 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 43. [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 43: 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.

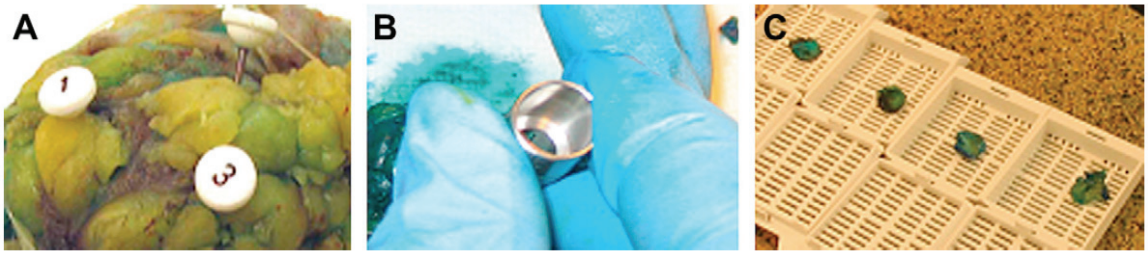
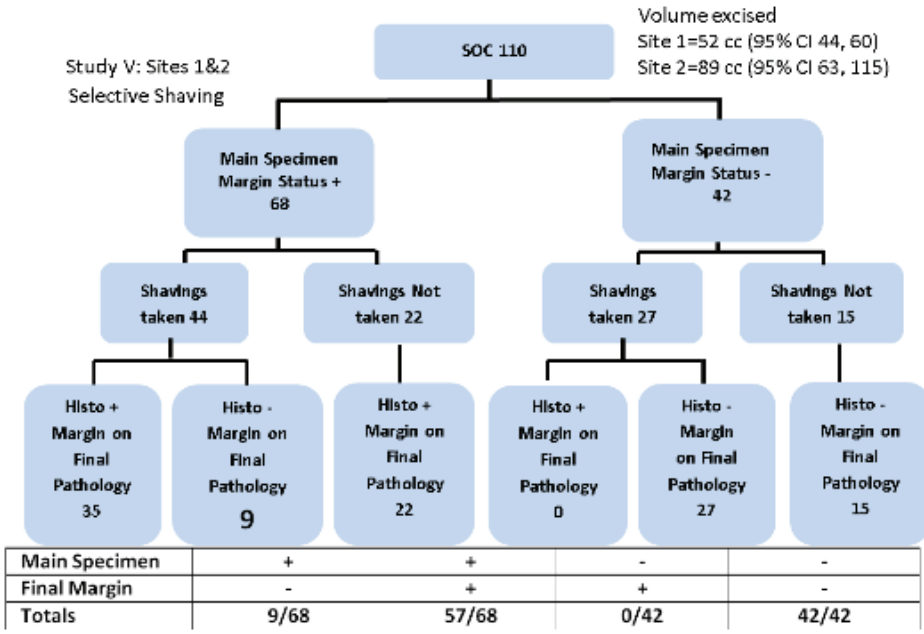


Figure 10 - Study V - Sampling Process

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).

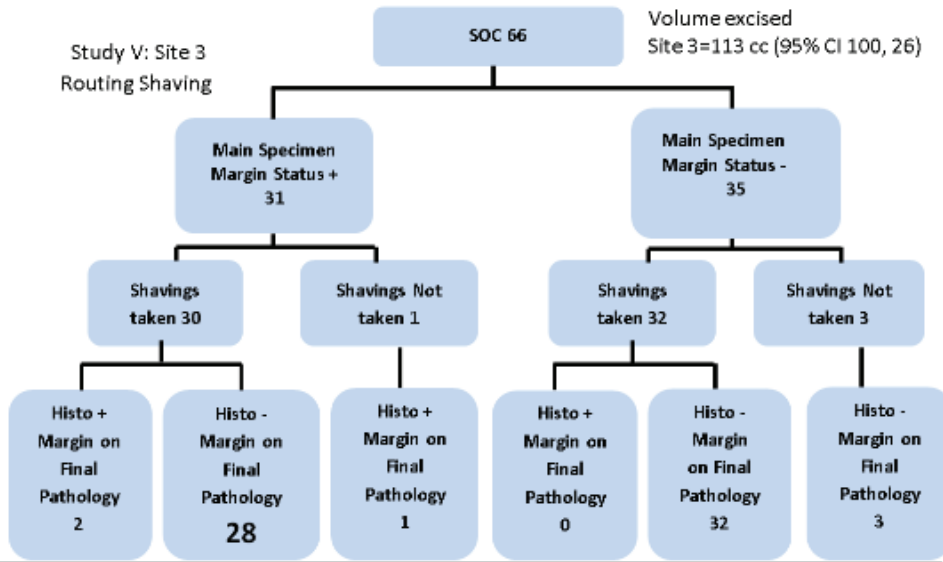
While results from Study V served to further inform the MarginProbe product development, Study V also serves to provide a comparison of differences in standard of care selective versus empiric total cavity shaving. Patients who receive empiric, routine re-excision of all margins have greater conversion of initial positive lumpectomy margins to final negative margins. The observed effect is illustrated below in Figures 11 and 12 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.



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

Figure 11 - Study V - Final Pathologies from Patients Treated at Study Sites 1 and 2 (Selective Re-excision)



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

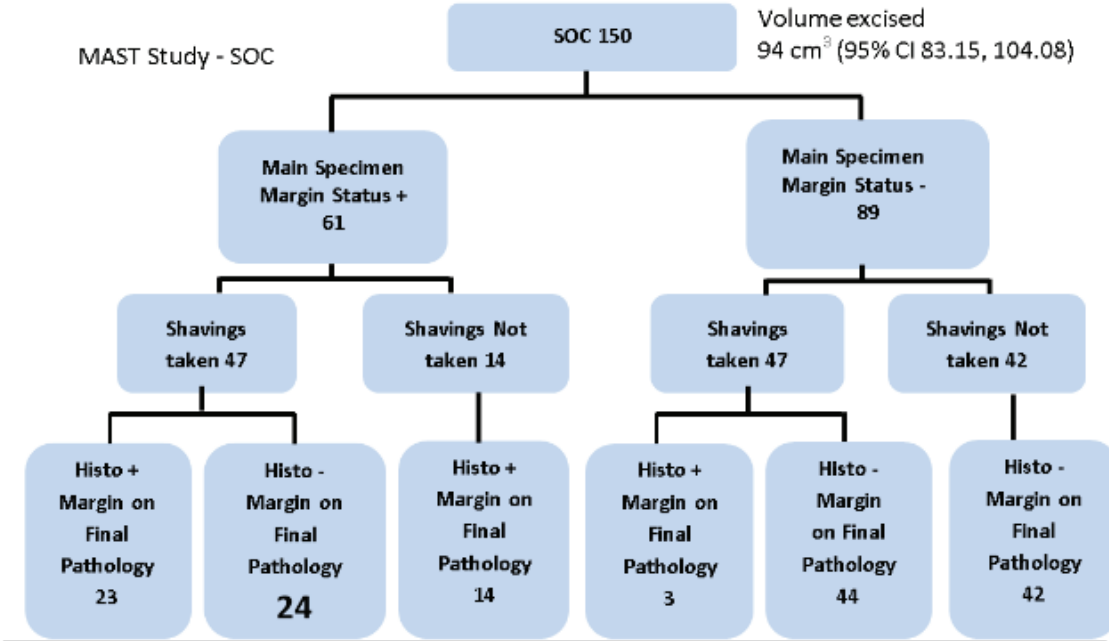
Figure 12 - Study V - Final Pathologies from Patients Treated at Study Site 3 (Total Re-excision)

3. MAST Study

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

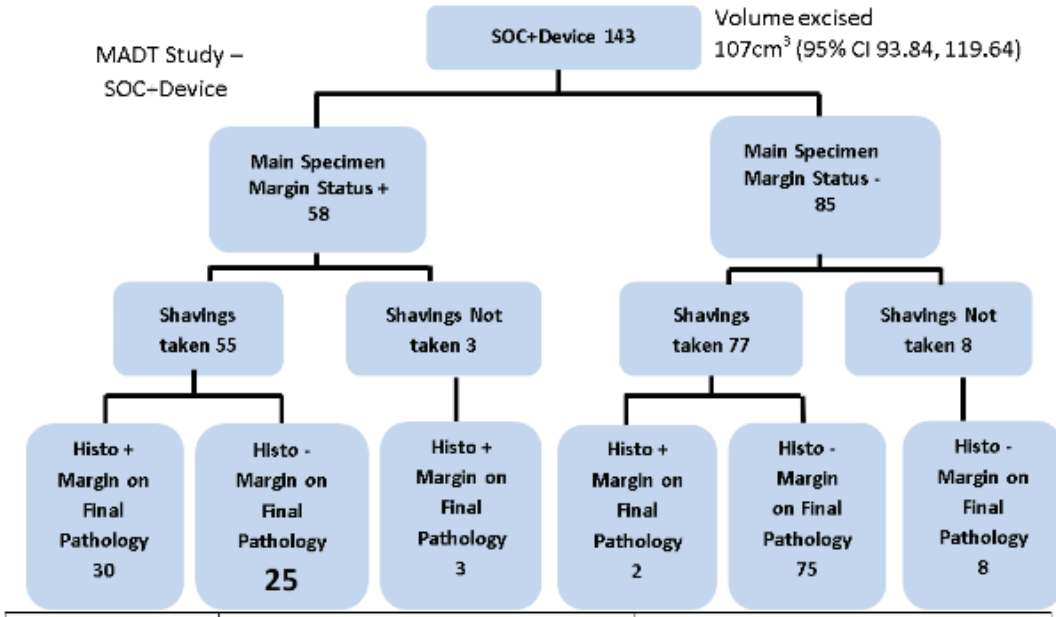
The MAST study design was similar to the Pivotal study however there were some differences. The MAST study involved a different MarginProbe device algorithm, different device use instructions (i.e. surgeons used the device at their discretion with respect to extent of device use and tissue targeted and 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 13 and 14 below.



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	39.3% (24/61)	60.7% (37/61)	3.4% (3/89)	69.6% (86/89)

Figure 13 - MAST Study - Final Pathologies - SOC Arm



Main Specimen	+		-	
Final Margin	-	+	+	-
Totals	43.1% (25/58)	56.9% (33/58)	2.4% (2/85)	97.6% (83/85)

Figure 14 - MAST Study - Final Pathologies - SOC+Device Arm

DIRECTIONS FOR USE

Set up Instructions

For complete instructions see the User Manual supplied with the MARGINPROBE® Console.

1. Turn on the console (see details in User Manual).
2. Open the sterile package in the sterile field, and remove the probe.
3. Make sure that the cables are straight and not twisted or bent.
4. Hand the connector outside the sterile field and connect to the console by plugging in and turning clockwise.
5. Make sure that the sensor tip is uncovered and is not in contact with tissue.
6. Calibration is performed automatically upon connection, as indicated on the screen. The probe is ready for use.

Instructions for Use

1. Before MarginProbe use, perform margin assessment and resection in accordance with standard of care practice.
2. In order to minimize probe exposure to local anesthetics, it is suggested that local anesthetics, if used, be used only at the skin incision point and incision path, and further used following device use.
3. MarginProbe is intended for use on freshly excised tissue within 20 minutes of tissue excision
4. It is suggested that the device not be used closer than 1.5 mm from localization guidewires, surgical clips, or other metallic instruments.
5. Blot the tissue to remove remnants and body fluids by using a sterile pad.
6. In order to prevent exposure of measured tissue to ultrasound gel before device use, device measurements may be performed before use of intraoperative ultrasound, or gel may be encapsulated (i.e., bagged).
7. Clearly mark the specimen orientation in accordance with standard pathological procedures.
8. An individual measurement is automatically triggered by applying the probe tip perpendicular to the tissue and ensuring stable contact for the suction holes in the perimeter. Once in contact with tissue, the tip is automatically attached by slight suction and a measurement is taken (see Figure 15 below).

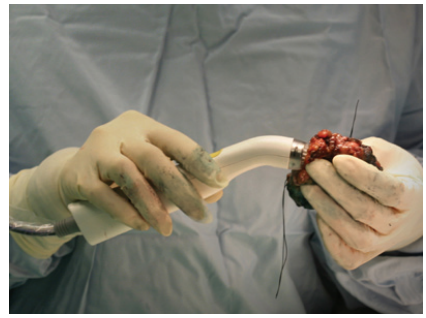


Figure 15: MARGINPROBE® **Probe Applied to Tissue**

9. Each individual measurement results in a binary positive/negative display on the console screen, as well as audio indication (see details in User Manual) (see Figure 16 below). Each measurement produces an audible sound and a bar on the screen: a blue bar and a double beep indicate a

negative measurement (normal tissue detected). A red bar and a single beep indicate a positive measurement (malignant tissue detected).

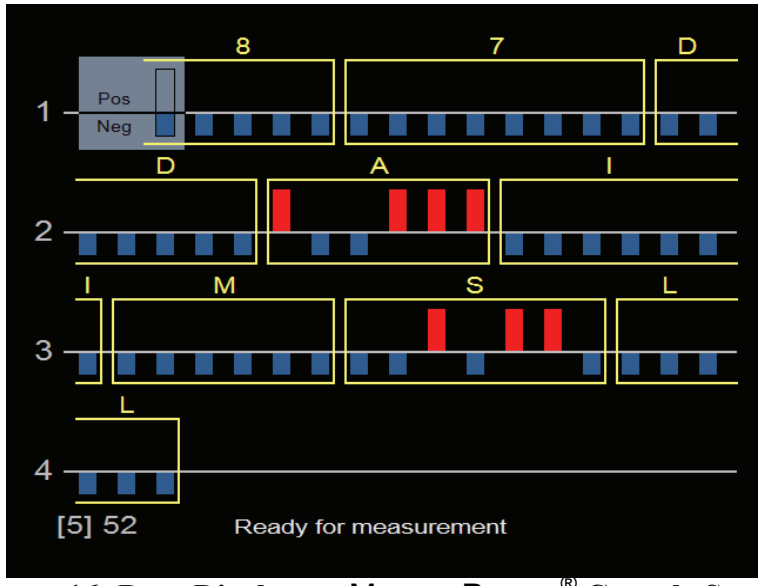


Figure 16: Data Display on MARGINPROBE® Console Screen

10. Failed measurements are indicated by a blank bar and an audible sound. If a measurement fails, the user should repeat the measurement.
11. After the audio indication has been heard, lift the probe. If the suction tip remains in contact with the tissue, additional measurements will be triggered.
12. Use the probe button to group individual readings into frames (see details in User Manual).
13. Multiple measurements are taken on the margin until the surface area of each margin has been measured (5-8 measurements per margin).
14. The display consists of individual readings grouped into named frames (as determined in item #8 above) and accumulates on the screen from left to right and top to bottom.
15. If any one of the device readings is positive, the margin should be considered positive, and an appropriate surgical action, consistent with standard practice, should be taken.
16. Document device use and collect and document information regarding the reason prompting cavity shavings. A sticker is provided with the probe, to assist with recording device readings.

Probe Troubleshooting

1. In the event the calibration is not indicated on the screen:
    - Hold the probe in the air and make sure the sensor is not covered.
    - Click the probe control button to restart calibration.
    - Follow screen instruction and replace the probe if required.
2. In the event that the suction does not work or there is otherwise believed to be poor tissue-probe contact:
    - Try to clear any visible tissue remnants that block the openings at the tip of the probe.
    - If problem persists, replace probe and contact Dilon Medical Technologies.
3. In the event of repeated failed readings:
    - Leave probe coupled to tissue until a beep is heard.
    - Ensure adequate coupling with proper suction by firmly holding probe tip perpendicular to tissue surface.
    - Assure that the probe tip is not placed over wires, clips or sutures.
    - Follow screen instructions and replace the probe if required.
    - If problem persists, contact Dilon Medical Technologies .
4. Circumstances warranting console servicing/replacement:
    - The initialization process does not start when turning on the console (a progress bar does not appear on the screen).
    - System is not ready for measurement after connecting the probe **Connect Probe** message persists after probe connection.

See Troubleshooting chapter of the MARGINPROBE® User Manual for Console Troubleshooting tips.

Training

On-site in-service orientation of surgical and OR staff will be performed.

Care and Maintenance

Console care and maintenance should be performed as instructed in the MARGINPROBE® User Manual, Chapter 7.

Contact information for equipment manufacturer:
Dilon Medical Technologies Ltd.
20 Alon Hatavor St. P.O.B 3131
Caesarea Ind. Park 3079519
Israel
www.dilon.com