SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Ultrasound Imaging Device

Device Trade Name: somo•v® Automated Breast Ultrasound System (ABUS)

Device Procode: PAA

Applicant's Name and Address: U-Systems, Inc.
447 Indio Way
Sunnyvale, CA 94085

Date(s) of Panel Recommendation: April 11, 2012

Premarket Approval Application (PMA) Number: P110006

Date of FDA Notice of Approval: September 18, 2012

Expedited: No

II. INDICATIONS FOR USE

The somo•v® Automated Breast Ultrasound System (ABUS) is indicated as an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (BI-RADS Assessment Category 1 or 2), with dense breast parenchyma (BI-RADS Composition/Density 3 or 4), and have not had previous clinical breast intervention. The device is intended to increase breast cancer detection in the described patient population.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the somo•v® Automated Breast Ultrasound System (ABUS) labeling.

V. DEVICE DESCRIPTION

The U-Systems somo·v Automated Breast Ultrasound System (ABUS) is designed to acquire B-mode ultrasound images using a linear transducer that is scanned over the breast, in an automated fashion, to collect Three Dimensional (3D) ultrasound volume data. The ultrasound component

of the device is called Scan Station. The system also provides three-dimensional (3D) image visualization capabilities, specifically allowing 2D, ultrasound-based images, reconstructed from the original scan set, in any desired orientation. The reconstructed images as well as the original linear B-mode images are presented to radiologists using the second component of the device (a remote Personal Computer (PC) workstation, equipped with the image-processing and visualization software), called somo·VIEWer Workstation. The 3D ultrasound dataset is available to the reader immediately after acquisition and at any future point in the course of a patient's care.

The ABUS device uses a fully automated process to capture image data from a 15.4cm x 17.0cm x 5.0cm volume of the breast in one minute. Up to 350 2D B-mode ultrasound images are collected using a high frequency linear transducer, and a large footprint of 15.4cm that allows the entire breast to be scanned in one sweep. The transducer is scanned automatically over a linear dimension of 17.0cm, providing an overall acoustic window of 15.4cm x 17.0cm over the breast. The B-mode images have a depth of up to 5.0cm from the anterior surface of the breast. The patient lies supine on a standard exam table in the supine position during scanning. An ultrasound lotion is used to maintain adequate coupling between the skin and the transducer. A disposable mesh membrane stabilizes the breast in place while the transducer automatically moves across it.

Upon completion of the scan, the 2D image data sets are sent either automatically by the ABUS device or manually by the operator to the remote somo·VIEWer Work Station. U-Systems software on the somo·VIEWer Work Station immediately converts the 2D image data sets to multi-planar 3-Dimensional (3D) reconstructed images for display on the somo·VIEWer Workstation to facilitate the review of the entire breast volume in three orthogonal planes (Coronal, Transverse, and Sagittal). The ABUS Scan Station, patient positioning, and transducer placement on the breast are shown below in Figure 1.

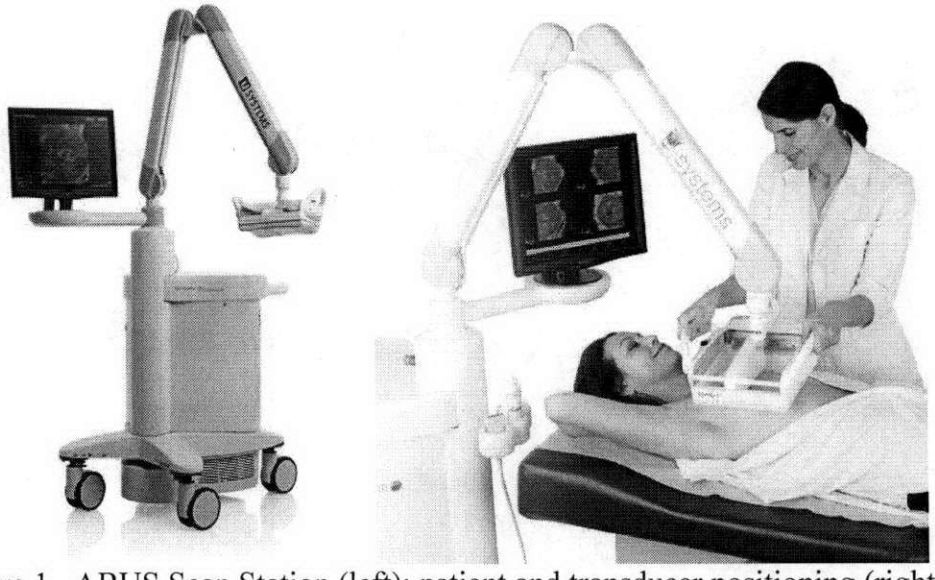

Figure 1. ABUS Scan Station (left); patient and transducer positioning (right)

The reconstructed 3D images are available for reading within minutes of acquisition. The digital multi-planar 3D display allows the operator to visualize the 3D positions of potential breast

abnormalities within the three dimensional anatomy of the breast tissue and to document the location of these abnormalities relative to the nipple, anterior skin surface and posterior chest wall. Figure 2 is a representative screen from the somo·VIEWer Work Station with superimposed annotation by the sponsor to indicate the cancer that was found in a 71-year old women with BI-RADS Assessment Category 1 or 2, with dense breast parenchyma (BI-RADS Composition/Density 3).

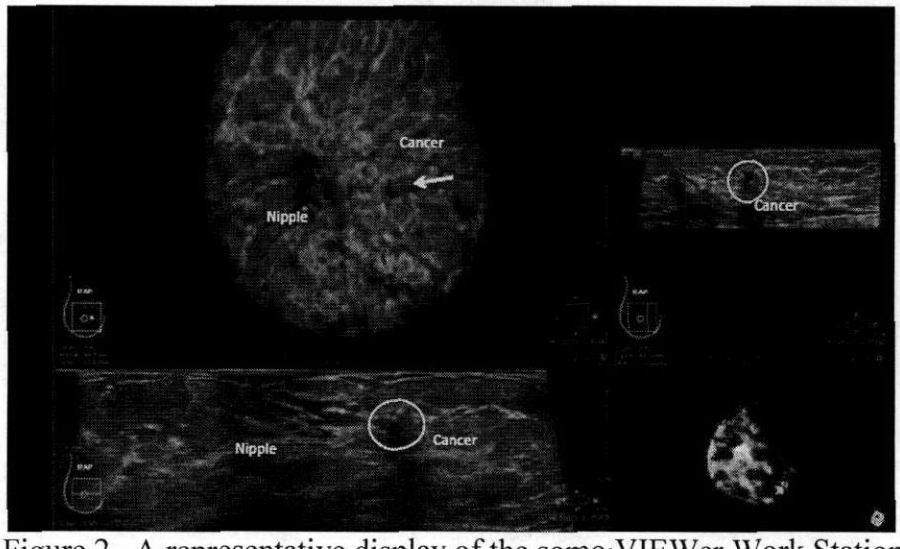

Figure 2. A representative display of the somo·VIEWer Work Station

The automation of breast ultrasound is intended to reduce operator dependence and increase the consistency, reproducibility, sensitivity, and reliability of each full breast ultrasound exam.

The ABUS is intended to be used in clinical practice as illustrated below in Figure:

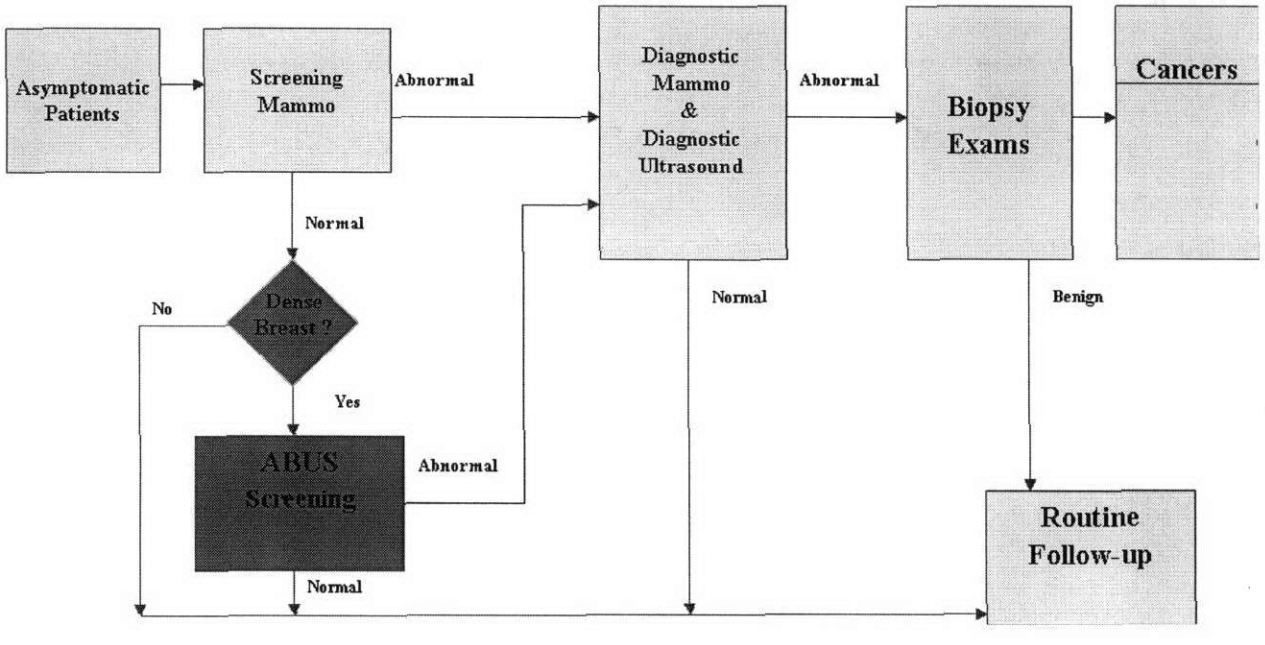

Figure 3. Flow chart demonstrating the use of ABUS as an adjunct to screening mammography.

The above chart demonstrates the use of the ABUS device as an adjunct to screening mammography, according to the proposed IFU statement. The ABUS device would be indicated for dense-breasted women who have had a negative screening mammogram. Subsequent to an ABUS examination, these women will have a routine follow-up if the ABUS results are negative. On the other hand, if the ABUS results are positive, these women will go to diagnostic workup, including diagnostic mammography and diagnostic handheld ultrasound. Based on this flow chart, ABUS would represent an additional step in the clinical practice of mammography, for dense-breasted women with negative mammography results. Furthermore, it should be noted that the ABUS device is not intended to be used as a replacement for diagnostic mammography or diagnostic handheld ultrasound.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

X-ray mammography (XRM) is the only imaging modality that is marketed and labeled for breast cancer screening. However, increased breast tissue density is the most significant factor limiting the effectiveness of mammographic screening, and approximately 40% of women who participate in organized mammography screening have dense breast tissue [1]. The sensitivity of mammography is reduced by 36% to 38% for women with dense breast tissue in comparison to the sensitivity of mammography for women with non-dense breast tissue, because dense breast tissue can conceal malignant lesions [2].

Currently, the alternative, non-invasive diagnosis methods for detection of breast cancer include Magnetic Resonance (MR), and handheld ultrasound imaging. While MR and ultrasound imaging are effective modalities in detection of breast cancer, they have limitations including availability, patient acceptance, length of scan, expense, etc. Furthermore, MRI may require contrast injection that is contraindicated in certain patient populations.

The ABUS is a first-of-a-kind device that offers automated breast ultrasound, as an adjunct to mammography for breast cancer screening in asymptomatic women. Currently, there is no ultrasound imaging system indicated for breast cancer screening.

VII. MARKETING HISTORY

ABUS device was originally cleared in 2005, and subsequently in 2008 as an adjunct to mammography for B-mode ultrasonic imaging of a patient's breast.
According to the sponsor, the ABUS device, indicated as an adjunct to mammography, has been marketed in the US since its FDA clearance in 2005. Also, the ABUS system is marketed under CE Mark since August 30, 2006, in Switzerland, Belgium, Portugal, Germany, and France, and in Taiwan under Import License since September 21, 2005. The ABUS system also has been licensed in Canada since September 21, 2007.

The device has not been withdrawn from any markets for any reason related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No adverse events have been reported for the ABUS device. Further, no adverse events have been reported for the subjects enrolled in the pivotal reader study. There are no identified direct risks to the safety or health of the patient or the physician with the use of the ABUS device. To date, researchers have not identified any adverse biological effects clearly caused by ultrasound operating at frequencies, intensities and exposure conditions of the ABUS.

Probable adverse effect on health could be in a false diagnosis, i.e. false positive and false negatives. A false positive test could lead to additional imaging evaluation and workup that would otherwise not be performed, leading to increased expense for the patient and a small risk of additional discomfort and complications. The consequences of a false negative would be a delay in diagnosis; however, this delay would happen for certain if the ABUS device were not used, as the device is indicated for women with negative mammograms who would otherwise have a mammogram in one year.

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical studies were conducted for the U-Systems Automated Breast Ultrasound System (ABUS) for FDA premarket clearance as components of the Verification and Validation process. The system described in the subject PMA is identical to the currently-cleared device, with the exception that software was added to the workstation to produce electronic Case Report Forms (eCRFs) for the conduct of the supporting Reader Study. This software for the eCRFs operated independently of ABUS system software and will not be included in commercial units. The ABUS System performance has been verified and validated according to the U-Systems Design Control Procedure, which is compliant with 21 CFR 820.30.

A. Laboratory Studies

All procedures were conducted in conformance with good laboratory practice and ISO 17025.

1. Thermal, Mechanical and Electrical Safety

The ABUS has been certified for compliance to UL 60601-1 & CSA-C22.2 by TUV Rheinland.

- Certificate of Conformity TUV CU72051803.01
- 9000-0019-01 Rev03 ABUS Regulatory Compliance Test Plan and Results.

Table 1. Thermal, Mechanical and Electrical Safety Testing

Test	Standard
Medical Electric Equipment Part 1: General Requirements for Safety	IEC 60601-1:1988 + A1:1991 + A2:1995
Medical Electrical Equipment Part 1-4: Collateral Standard:	IEC 60601-1-4: 1996 (First Ed.) + Am.1:

Programmable Electrical Medical Systems	1999 (Consolidated 1.1 Ed.) for use with IEC 60601-1 (1988), Amts 1 (1991) and 2 (1995)
Medical Electrical Equipment – Part 2: Particular Requirements for the Safety of Ultrasonic Medical Diagnostic and Monitoring Equipment	IEC 60601-2-37:2001+ A1: 2004 + A2: 2005 for use in conjunction with IEC 60601-1:1988 + A1: 1991 + A2:1995
Medical Electrical Equipment - Part 1: General Requirements for Safety 2. Collateral Standard: Electromagnetic Compatibility - Requirements and Tests	93/42/EEC EN 60601-1-2 2001

2. Biocompatibility

To verify the biocompatibility of the ABUS patient contact materials, U-Systems conducted biocompatibility testing pursuant to FDA's Guidance Document (#G95-1), Use of International Standard ISO-10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (1995)", which specifically outlines the types of biocompatibility tests that are required based on the nature of the device and the extent and duration of its contact with blood or tissues. The studies were conducted under approved protocols and the results were reviewed and approved by the contract laboratory and U-Systems, Inc. According to the FDA guidance and ISO standards, the ABUS Transducer is a "surface device" in contact with the skin for limited exposure (<24 hour) during ultrasound imaging procedures. Based on these characteristics, the following biocompatibility tests were performed:

- Cytotoxicity - MEM Elution, L929 Cells
- Irritation - ISO Intracutaneous Reactivity
- Sensitization - ISO Guinea Pig Maximization Sensitization

The ABUS materials passed the above testing demonstrating the biocompatibility of the patient skin contact materials.

3. Acoustic Output

Acoustic Output Tables are provided in Appendix A of the ABUS Scan Station User's Manual (4700-0006-02). The Medical Ultrasound Safety Manual, licensed from AIUM, is also included in the ABUS Scan Station User's Manual. No system/transducer combination is capable of exceeding, or has exceeded, either a TI of 1.0 and MI of 1.0 in any operating mode.

B. Animal Studies

No Animal Studies were conducted to support the safe and effective use of ABUS.

C. Additional Studies

U-Systems has provided a conformance statement that the Automated Breast Ultrasound System is designed and marketed in conformance with the Output Display Standard entitled "Measurement Methodology for Mechanical and Thermal Indices". ***"Standard For Real-Time Display Of Thermal And Mechanical Acoustic Output Indices On Diagnostic Ultrasound Equipment Revision 2"*** **(NEMA UD-3 2004).** (MI is displayed with B mode imaging).

U-Systems has provided a conformance statement that the measurements of acoustic output display indices – the Mechanical Index (MI) - are made per Section 6 of the Output Display Standard entitled "Measurement Methodology for Mechanical and Thermal Indices". ***"Standard For Real-Time Display Of Thermal And Mechanical Acoustic Output Indices On Diagnostic Ultrasound Equipment Revision 2"*** **(NEMA UD-3 2004).**

X. SUMMARY OF PRIMARY CLINICAL STUDIES

U-Systems conducted an observational case-controlled, multi-reader, multi-case (MRMC) Receiver Operating Characteristic (ROC) study (the pivotal Clinical Retrospective Reader Study (CRRS-4)), to support the use of its ABUS device for the proposed indications for use.

A. Study Design

The pivotal study took place between July 16, 2011 through August 5, 2011. The database for this PMA reflected data collected through June 3, 2011 and included 200 patients. Seventeen (17) qualified readers participated in the pivotal study. Data was collected from 13 data collection sites.

Prior to the pivotal study, U-Systems conducted three non-pivotal studies (CRRS-1, CRRS-2, and CRRS-3) that we used to refine the design of the pivotal study. Table 2, below, provides a summary of the clinical studies.

Table 2. Summary of the Clinical Studies

	CRRS-1*	**CRRS-2***	**CRRS-3****	**CRRS-4**
Objective	To evaluate reader performance with ABUS+XRM vs. XRM Alone in asymptomatic women with >50% parenchymal density (BI-RADS Composition/Density rating of 3 or 4).		To determine the impact on reader performance, as defined by the ROC Area Under Curve (AUC) with ABUS+XRM vs. XRM Alone in asymptomatic women with >50% parenchymal density (BI-RADS Composition/Density rating of 3 or 4) and a screening mammogram assigned a BI-RADS Assessment Category 1 (negative) or 2 (normal with benign	

Table 2. Summary of the Clinical Studies				
	CRRS-1*	**CRRS-2***	**CRRS-3****	**CRRS-4**
			findings).	
Study Design	All studies employed a Multi-reader multi-case (MRMC) ROC study design.			
Cases, Readers and Primary Analysis	Case Sets: XRM alone; XRM+XRM; XRM+ABUS	The Pivotal CRRS-4 Study, as well as non-pivotal CRRS-2 and CRRS-3 studies evaluated the following Case Sets: XRM alone; XRM+ABUS		
	300 cases included asymptomatic Non-Cancer cases, asymptomatic pathologically confirmed Cancer cases and symptomatic Cancer cases.	308 cases included asymptomatic Non-Cancer cases, asymptomatic pathologically confirmed Cancer cases and symptomatic Cancer cases.	200 cases included asymptomatic Non-Cancer cases, asymptomatic pathologically confirmed Cancer cases.	200 cases included asymptomatic Non-Cancer cases, asymptomatic pathologically confirmed Cancer cases.
	Primary data analysis was performed on image readings by 12 readers for cases from both asymptomatic and symptomatic women with both mammo-negative and mammo-positive exams.	Primary data analysis was performed on image readings by 3 readers for cases from both asymptomatic and symptomatic women with both mammo-negative and mammo-positive exams.	Primary data analysis was performed on image readings by 13 readers for cases from asymptomatic women with negative/normal mammography exams.	Primary data analysis was performed on image readings by 17 readers, who did not participate in CRRS-3 study, for cases from asymptomatic women with negative/normal mammography exams.
Primary End Point	Difference in the areas under the Receiver Operating Characteristic (ROC) curves (AUC) for XRM Alone compared to that computed for XRM+ABUS.		Difference in the areas under the Receiver Operating Characteristic (ROC) curves (AUC) computed using the trapezoidal rule for XRM Alone compared to that computed for XRM+ABUS.	

* CRRS-1 and CRRS-2 were submitted in a pre-IDE to the Agency. CRRS-1 was statistically powered for AUC difference between modalities (XRM, XRM+ABUS). Unlike pivotal study

CRRS-4, cases with negative/normal mammography exams were not excluded.
** CRRS-3 was originally a pivotal study, which was not filed for review by FDA because the study population did not match the intended patient population for their device.

The cases for all studies were retrospectively selected from an ongoing prospective multi-center registry study which was not designed to demonstrate the safety and effectiveness of the ABUS system for its proposed indication for use. Most of the cancer cases in the prospective study were shared across the four studies and some non-cancer cases were also shared, but the sets of readers used in each study were mutually exclusive.

1. Clinical Inclusion and Exclusion Criteria

Prospective multi-center registry study, USI2008002:

The cases for the pivotal study were retrospectively selected subset from an ongoing prospective multi-center registry study, USI2008002. Patients enrolled in the registry study USI2008002 provided informed consent prior to enrollment and received both XRM and ABUS at study entry as part of their annual routine screening exam. A clinical site investigator at the clinical site performed the interpretation of the XRM and ABUS exams for each patient. All suspicious abnormalities identified on XRM or ABUS received a complete diagnostic evaluation.

Enrollment in the USI2008002 study was limited to subjects who met the following inclusion criteria:

- Female,
- Age 25 or older,
- Asymptomatic (by patient self-report, patient self-breast exam or clinical breast exam)
- >50% parenchymal density on XRM at study entry,

Patients were not permitted to enroll in the USI2008002 study if they met any of the following exclusion criteria:

- Currently pregnant or breastfeeding,
- Planning to become pregnant in the following 15 months,
- Any breast surgeries or interventional procedures in the past 12 months,
- Any history of cancer diagnosis and/or treatment in the past 12 months.

Pivotal Study Patient Population:

The pivotal study included 200 breast screening cases from USI2008002, of which 164 were included in the primary analysis (31 cancer and 133 non-cancer, as defined below). The primary data analysis set consisted of XRM and XRM+ABUS images from asymptomatic females with >50% parenchymal density for whom the XRM screening mammogram was assigned a BI-RADS Assessment Category 1 or 2. Both the parenchymal density assessment and the BI-RADS Assessment Category were provided by the registry clinical site investigator at the time of initial review at study entry in USI2008002.

There were 36 (164+36=200) supplemental and control cases interspersed with the

primary data cases during the image reading sessions to ensure that the experimental reader setting included a case mix that is closer to that in clinical practice, although approximating the case mix for typical clinical practice is not possible. By study design, these cases were not to be included in the study analyses. Among these 36 cases, 21 were XRM-positive cancer cases (XRM BI-RADS 0 or 3) to ensure the reader's vigilance. Also, 15 cases did not have a paired ABUS image to ensure that the readers remain vigilant in the initial reading of XRM alone (12 were non-cancer cases with XRM BI-RADS 1 or 2, and the remaining 3 were cancer cases with XRM BI-RADS 0 or 3). Table 3, below, shows the grouping of the 200 cases.

Table 3. Grouping of the 200 cases used in the pivotal study

Digital Imaging Modalities Required for a Complete Case	**Non-Cancer Cases XRM Assigned BI-RADS 1 or 2**	**Cancer Cases XRM Assigned BI-RADS 1 or 2**	**Cancer Cases XRM Assigned BI-RADS 0 or 3**
XRM+ABUS Complete Case	133* Group N	31* Group A	21** Group B
XRM Only (Control Cases)	12** Group C	0	3** Group D

** Cases in Primary Analysis*

*** Supplemental and Control Cases*

Inclusion Criteria:

The primary data analysis set of 164 cases for the pivotal study met all of the following inclusion criteria:

- All Inclusion criteria for Registry Study Protocol USI 2008002, (see above),
- BI-RADS Composition/Density of 3 or 4 as assessed by the registry clinical site investigator during the initial XRM reading at study entry,
- Evaluable bilateral CC and MLO views available for XRM exam,
- XRM assigned a BI-RADS Assessment Category 1 or 2 by the registry clinical site investigator at the time of initial reading at study entry,
- Evaluable bilateral AP, LAT and MED views available for ABUS exam,
- For cancer cases, membership in Class 1 (defined below),
- For non-cancer cases, membership in Class 2, 3, 4, or 5 (defined below),
- No significant protocol deviations that could be expected to bias reader interpretation,
- Available source records for verification purposes, and
- Complete Electronic Data Capture records.

Exclusion Criteria:

The primary data analysis set of 164 cases for the pivotal study did not meet any of the following exclusion criteria:

- XRM assigned a BI-RADS Assessment Category 0 or 3 by the registry clinical site investigator at the time of initial reading at study entry,
- XRM assessed a BI-RADS Composition/Density score of 1 or 2 (<50% parenchymal density), by the registry clinical site investigator at the time of initial

reading at study entry,

- For non-cancer cases (defined below), a relevant medical history or existing benign breast findings, which could otherwise be classified as abnormal without knowledge of said history, access to relevant clinical data or review of prior images, including but not limited to prior history of breast interventional procedures, such as breast enhancement surgery, breast biopsy or cyst aspiration, mastectomy and lumpectomy as well as history of breast radiation or breast cancer,
- Cases demonstrating administrative or technical errors, for example:
  - o XRM or ABUS image data not available on internal storage server,
  - o XRM or ABUS exam incomplete or missing views,
  - o XRM or ABUS image data file corrupted or incompatible with workstation review, and
  - o XRM or ABUS image quality inadequate due to technologist error in labeling or positioning or acquisition technique.

Case Selection:
A consecutive series of cases that satisfied the inclusion and exclusion criteria were eligible candidate cases for the pivotal study.

a. Cancer cases: All cases from the consecutive series that belonged to class 1 defined below were employed as cancer cases in the pivotal study:

- Class 1: Cases in which biopsy-proven breast cancer was identified at most 365 days after the original screening mammogram through any modality or workup for any reason.

b. Non-cancer cases: All cases from the consecutive series that did not satisfy the Class 1 requirements were considered non-cancer candidate cases. These cases were pooled for potential inclusion in the non-cancer case set if the original screening mammogram was performed at least 365 days prior to the date the cases were randomly sampled for use in the pivotal study. A random sample from this consecutive group of non-cancer cases across thirteen clinical sites was used. This group of non-cancer cases was comprised of cases in the following classes

- Class 2: Follow-up-confirmed cases with no breast cancer found by a follow-up exam that occurred at most 365 days after the original screening mammogram.
- Class 3: Follow-up confirmed cases where a biopsy-proven breast cancer was identified more than 365 days after the original screening mammogram.
- Class 4: Follow-up-confirmed cases with no breast cancer found at annual follow-up exam, where the annual follow-up exam occurred after 365 days after the original screening mammogram.
- Class 5: Cases with no follow-up; Unverified cases for which no follow-up confirmation regarding the presence or absence of breast cancer could be obtained.

Classes 1 through 5 are mutually exclusive, i.e. there is no overlap between classes.

Readers and reader training:

The readers for the clinical study were interpreting physicians, as defined under 21 CFR 900.12(a)(1)(i)(B)(2), who additionally were fellowship-trained in breast imaging and/or had 10 years of experience in breast imaging in a practice that is at least 70% breast imaging. Furthermore, the readers met the minimum mammography interpretation requirements per Mammography Quality Standards Act (MQSA), and had a review rate of at least 1,000 mammograms annually for the year prior to study participation, as well as a review rate of at least 500 breast ultrasound exams annually for the year prior to study participation. Overall, 61 radiologists were solicited by U-systems for the study, and 33 met the criteria. Based on their availability during the study dates, 17 readers were selected to participate. The readers practiced in academia (7), private (6), or community clinics (4).

The readers successfully completed ABUS training. The training consisted of three training modules conducted over a period of 1-3 weeks. The three modules consisted of Module I, a self-study activity of five online tutorials including case study presentations, Module II, an interactive, real-time webinar with an ABUS expert (U-Systems representative) to review teaching case studies on detection of breast cancer, and Module III, a ten-hour training at the U-Systems headquarters on ABUS technology, including hands-on sessions with the somo-VIEWer workstation. Module III also included a discussion of general teaching cases that represented the range of typical anatomy and abnormalities identified using ABUS, followed by independent review of cases by the readers. Subsequently, the faculty instructor reviewed each case with each reviewer. At the conclusion of the training, each reader was required to pass a skill set exercise that included 25 cases (10 biopsy-confirmed cancers, 10 benign biopsy-confirmed lesions, and 5 negative cases), with a score of 100%.

Image Interpretation:
The readers first interpreted the case images for XRM Alone and recorded their image readings on an electronic case report form. Upon completing the reading for XRM Alone, the reader then reviewed the ABUS exam together with the XRM, after which a second reading for XRM+ABUS was recorded. XRM images were viewed on an MQSA approved workstation and ABUS images were viewed on the somo-VIEWer Workstation.

For each reading condition, the reader provided an initial BI-RADS assessment category of 0 or 1 or 2, and a likelihood of malignancy between 0% and 100% (for the ROC analysis). If an initial BIRADS of 0 is given, the reader also assigned a forced (7-point) BI-RADS Assessment Category of 1-3, 4a-c, or 5. The reader also electronically marked any regions of interest that were suspicious for cancer.

Lesion Location:
The location data applies exclusively to the location-specific sensitivity analysis and does not apply to the primary case-level ROC analysis. Two board-certified "gold standard" (GS) radiologists independently reviewed all cancer cases. Using all available source records for each cancer case, the GS radiologists independently confirmed the true location of the malignancy within the screening mammogram and ABUS images, and

marked the X, Y (mammogram) or X, Y, Z (ABUS) coordinates for its location. In the event of discordance between the two GS radiologists, an additional visual inspection of the region of interest was performed by one of the radiologists.

The markers placed by the readers on each of the XRM and ABUS images in the CRRS-4 study were compared to and scored against the final truth file in order to determine lesion sensitivity by location from the readers' XRM and ABUS markings of each cancer lesion. For a detection to occur, the Euclidean distance between the Truth X,Y or X, Y, Z location and the reader indicated X,Y or X, Y, Z lesion location, respectively, had to be less than or equal to the maximum of [15 mm, Final Target size/2].

2. Follow-up Schedule
   Subjects who were not diagnosed with breast cancer from a workup for any reason were/are followed for approximately 12 months, until their next routine screening exam, at which point they received a standard XRM exam.

3. Study Endpoints
   The primary endpoint of the pivotal study was the difference in the areas under the Receiver Operating Characteristic (ROC) curves (AUC) computed using the trapezoidal rule for XRM Alone compared to that computed for XRM+ABUS.

   A secondary set of endpoints were reader sensitivity and specificity for XRM+ABUS compared to XRM Alone, with cut points of BI-RADS 4a and BI-RADS 3.

B. Accountability of PMA Cohort

This section does not apply for the type of retrospective reader study used in the pivotal study of this PMA.

C. Study Population Demographics and Baseline Parameters

Table 4 summarizes patient demographics and clinical characteristics. The mean age was 54.0 years (standard deviation of 10.8). The majority of patients were White (82.3%), with 6.7% indicating Black/African American/Haitian, 6.1 % indicating Asian, 4.9% indicating Hispanic/Latina/Spanish, 1.8% indicating Other/Unknown, 0.6% indicating American Indian/Alaska Native, and 0.0% indicating Native Hawaiian/Pacific Islander. The mean (± standard deviation) was 64.5 ± 2.6 inches for height, 141.0 ±26.7 pounds for weight, and 24.1 ±4.4 kg/m^2 for body mass index (BMI). The most frequent bra size reported was 34 (39.3%), followed by 36 (38.7%), 38 (11.0%), 32 (7.4%), 40 (1.8%), and other bra sizes (1.8%). The most common bra cup size was B (38.5%), followed by C (28.6%), A (15.5%),0 (11.2%), DD (5.0%), and other cup sizes (1.2%). Of the cancer cases, 48.4% reported having any previous breast treatment or procedure (the most common being biopsy; categories not mutually exclusive), while only 1 (0.8%) of the non-cancer cases indicated a previous breast treatment or procedure. With respect to personal history and family history, 1.8% of patients reported having ever been diagnosed with breast cancer, 40.9 % reported having a family history or breast cancer, 39.6% reported still having natural menstrual periods, 10.4%

reported having any Ashkenazi Jewish descent (the most common being lineage from the grandmother and/or grandfather; categories not mutually exclusive). No cases reported having the BRCAI or BRCA2 gene.

Table 4. Patient Demographics and Clinical Characteristics			
Characteristic	Non-Cancer cases N=133	Cancer cases N=31	Total N=164
Age (years), Mean ±SD	52.8 ±1 0.5	59.4 ± 10.4	54.0 ±10.8
Ethnic / racial background, N (%)*			
Hispanic/Latina/Spanish	6 (4.5%)	2 (6.5%)	8 (4.9%)
American Indian/Alaska Native	1 (0.8%)	0 (0.0%)	1 (0.6%)
Asian	7 (5.3%)	3 (9.7%)	10 (6.1%)
Black/African American/Haitian	10 (7.5%)	1 (3.2%)	11 (6.7%)
Native Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	111 (83.5%)	24 (77.4%)	135 (82.3%)
Unknown/Other	1 (0.8%)	2 (6.5%)	3 (1.8%)
Height (inches), Mean ± SD	64.4 ± 2.6	64.9 ± 2.7	64.5 ± 2.6
Weight (pounds), Mean ± SD	140.6 ± 28.0	142.7 ± 20.7	141.0 ± 26.7
BMI (kg/m^2), Mean ± SD	24.1±4.7	24.0 ± 3.3	24.1 ± 4.4
Bra size, N (%)			
32	12(9.1%)	0 (0.0%)	12 (7.4%)
34	52 (39.4%)	12 (38.7%)	64 (39.3%)
36	46 (34.8%)	17 (54.8%)	63 (38.7%)
38	16 (12.1 %)	2 (6.5%)	18 (11.0%)
40	3 (2.3%)	0 (0.0%)	3 (1.8%)
Other	3 (2.3%)	0 (0.0%)	3 (1.8%)
Bra cup size, N (%)			
A	19 (14.6%)	6 (19.4%)	25 (15.5%)
B	51 (39.2%)	11 (35.5%)	62 (38.5%)
C	37 (28.5%)	9 (29.0%)	46 (28.6%)
D	14 (10.8%)	4 (12.9%)	18 (11.2%)

DD	7 (5.4%)	1 (3.2%)	8 (5.0%)
Other	2 (1.5%)	0 (0.0%)	2 (1.2%)
Ever diagnosed with breast cancer, N (%)			
Yes	0 (0.0%)	3 (9.7%)	3 (1.8%)
No	133(100.0%)	28 (90.3%)	161 (98.2%)
Breast treatments or procedures, N (%)			
Cyst aspiration	0 (0.0%)	5 (16.1%)	5 (3.0%)
Biopsy	1 (0.8%)	13 (41. 9%)	14 (8.5%)
Lumpectomy	0 (0.0%)	3 (9.7%)	3 (1.8%)
Mastectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Radiation	0 (0.0%)	2 (6.5%)	2 (1.2%)
None of these	132 (99.2%)	16 (51.6%)	148 (90.2%)
Still have natural menstrual periods, N (%)			
Yes	59 (44.4%)	6 (19.4%)	65 (39.6%)
No	69 (51.9%)	24 (77.4%)	93 (56.7%)
Not sure	5 (3.8%)	1 (3.2%)	6 (3.7%)
Family history of breast cancer, N (%)			
Yes	52 (39.1 %)	15 (48.4%)	67 (40.9%)
No	81 (60.9%)	16 (51.6%)	97 (59.1 %)
Ashkenazi Jewish descent, N (%)*			
None of these	118 (88.7%)	29 (93.5%)	147 (89.6%)
Mother	11 (8.3%)	2 (6.5%)	13 (7.9%)
Father	9 (6.8%)	2 (6.5%)	11 (6.7%)
Grandmother(s)	13 (9.8%)	2 (6.5%)	15 (9.1%)
Grandfather(s)	13 (9.8%)	2 (6.5%)	15 (9.1%)
BRCA1 or BRCA2 gene, N (%)			
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	132 (99.2%)	31 (100.0%)	163 (99.4%)
Missing	1 (0.8%)	0 (0.0%)	1 (0.6%)

* Categories are not mutually exclusive and may not sum to 100%.

Characteristics of malignancies among cancer cases are summarized in Table 5 below. Overall, 31 cancer cases were included in the primary analyses.

Table 5. Summary of Cancer Case Characteristics		
Characteristic	Total (N=31)	Total (N=16) †
Type based on XRM, N (%)	N (%)*	N (%)**
Architectural Distortion	5 (15.6%)	3 (17.7%)
Architectural Distortion and Mass	1 (3.1%)	0 (0.0%)
Asymmetric Density	1 (3.1%)	1 (5.9%)
Calcification	3 (9.4%)	1 (5.9%)
Mass	6 (18.8%)	3 (17.7%)
Occult	16 (50.0%)	9 (52.9%)
Type based on ABUS, N (%)	N (%)*	N (%)**
Architectural Distortion	0 (0.0%)	0 (0.0%)
Architectural Distortion and Mass	0 (0.0%)	0 (0.0%)
Asymmetric Density	0 (0.0%)	0 (0.0%)
Calcification	0 (0.0%)	0 (0.0%)
Mass	32 (100.0%)	17 (100.0%)
Occult	0 (0.0%)	0 (0.0%)
BI - RADS Density, N (%)		
3	20 (64.5%)	11 (68.8%)
4	11 (35.5%)	5 (31.3%)
Location, N (%)		
Right breast	18 (58.1%)	8 (50.0%)
Left breast	13 (41.9%)	8 (50.0%)
Region, N	N*	N**
Posterior	6 (18.8%)	3 (17.7%)
Middle	18 (56.3%)	10 (58.8%)
Anterior	8 (25.0%)	4 (23.5%)
Quadrant Location, N (%)	N (%)*	N (%)**
Left UOQ	5 (15.6%)	2 (11.8%)
Left LOQ	1 (3.1%)	1 (5.9%)
Left LIQ	0 (0.0%)	0 (0.0%)
Left UIQ	2 (6.3%)	1 (5.9%)
Left Retroareolar	1 (3.1%)	1 (5.9%)
Left Superior	0 (0.0%)	0 (0.0%)
Left Lateral	3 (9.4%)	3 (17.7%)
Left Inferior	0 (0.0%)	0 (0.0%)
Left Medial	1 (3.1%)	0 (0.0%)
Right UIQ	3 (9.4%)	2 (11.8%)
Right LIQ	1 (3.1%)	1 (5.9%)
Right LOQ	4 (12.5%)	1 (5.9%)

Right UOQ	5 (15.6%)	3 (17.7%)
Right Retroareolar	0 (0.0%)	0 (0.0%)
Right Superior	3 (9.4%)	1 (5.9%)
Right Lateral	3 (9.4%)	1 (5.9%)
Right Inferior	0 (0.0%)	0 (0.0%)
Right Medial	0 (0.0%)	0 (0.0%)
Max Diameter (mm)*, Mean + SD	13.0 ± 6.6	14.6 ± 7.3

* Out of 32 lesions (1 multifocal case).

** Out of 17 lesions (1 multifocal case).

† Summaries in the last column are for subjects with no prior breast interventions (see section entitled "Exclusion of subjects with prior breast interventions" below).

Table 6, below, shows the clinical sites, as well the number of cases in difference classes used for the pivotal study.

Table 6. Clinical sites and the number of cancer and non-cancer cases in each site

Name	State	Number of Cancer cases	Number of Non-Cancer cases	Total cases
Boca Raton Community Hospital - Deerfield	FL	0	3	3
Boca Raton Community Hospital - Meadows	FL	3	25	28
Community Hospital of the Monterey Peninsula	CA	6	21	27
George Washington University Medical Center	DC	6	22	28
Henry Ford Hospital System	MI	3	0	3
Kansas University Medical Center	KS	5	11	16
Radiology Regional Center – Del Prado	FL	1	4	5
Radiology Regional Center - Winkler	FL	1	11	12
Solis Women's Health	CA	1	1	2
Susan G. Komen Breast Center	IL	3	13	16
University of Texas Southwestern	TX	0	7	7
Virginia Mason Medical Center	WA	2	7	9
Women's Imaging Centre, Lafayette	LA	0	8	8
Total		31	133	164

Table 7, below, describes the readers' experience and qualifications. The 17 readers participating in the pivotal study reflected a broad range of experience, practice settings, and standard equipment used. Reader geographic location was represented by 8 states from the United States (California, Texas, Connecticut, Utah, West Virginia, North Carolina, Massachusetts, and Michigan) as well as 1 from Canada (Ontario). Reader experience in breast imaging

ranged from 2 to 18 years, and 9 of the 17 readers were fellowship trained in breast imaging. The number of mammography reads per year ranged from 1850 to 14,600 (mean: 5491), and the number of hand held ultrasounds per year ranged from 603 to 5000 (mean: 1285). All readers passed the ABUS interpretation skill exercise during the training. The results from all readers were included in the analysis.

Table 7. Summary of Reader Experience and Qualifications

Reader	Practice Category	Breast Imaging Fellowship Trained	Years in Breast Imaging	Mammography Review Rate/Yr	Hand-Held US Review Rate/Yr
1	Academic	YES	3	6,835	884
2	Private	YES	9	13,964	2,279
3	Private	NO	15	2,000	825
4	Community	YES	4	5,400	1,800
5	Academic	YES	2	2,500	800
6	Academic	YES	12	2,125	938
7	Academic	YES	18	3,283	643
8	Private	NO	16	8,820	743
9	Academic	YES	12	2,259	707
10	Community	YES	3	2,500	1,600
11	Private	YES	16	1,850	1,150
12	Community	NO	14	4,525	603
13	Private	NO	17	10,000	5,000
14	Private	NO	10	4,180	620
15	Academic	NO	18	14,600	1,750
16	Community	NO	10	5,500	750
17	Academic	NO	12	3,000	750

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the retrospective study in 200 patients. The key safety outcomes for this study are presented below. There are no adverse effects as indicated below.

Adverse effects that occurred in the PMA clinical study:

There were no adverse events reported by the Interpreting Physicians (Readers) or Principal Investigator as part of the Pivotal Clinical Retrospective Reader Study.

2. Effectiveness Results

The analysis of effectiveness was based on the retrospective study in 200 patients.

Primary Analysis: Area under the ROC curve (AUC)

The mean AUC values and associated standard errors within and between modalities

across all readers were derived under the Dorfman-Berbaum-Metz (DBM) approach (the original method is described in Dorfman, Berbaum, Metz, 1992 Invest Radiol 27(9):723-31) which assumes a mixed-effects ANOVA model for jackknife pseudovalues of AUC. Reader-averaged trapezoidal area was reported as 0.604 (95% CI: 0.535, 0.672) for XRM Alone and as 0.747 (95% CI: 0.671, 0.822) for XRM+ABUS. The difference of 0.143 was statistically significant (95% CI: 0.074, 0.212).

The overall ROC curves averaged across all readers' trapezoidal ROC curves are shown in Figure 4. For the trapezoidal curves, the sensitivity was averaged for every interval of 0.01 on the x-axis.

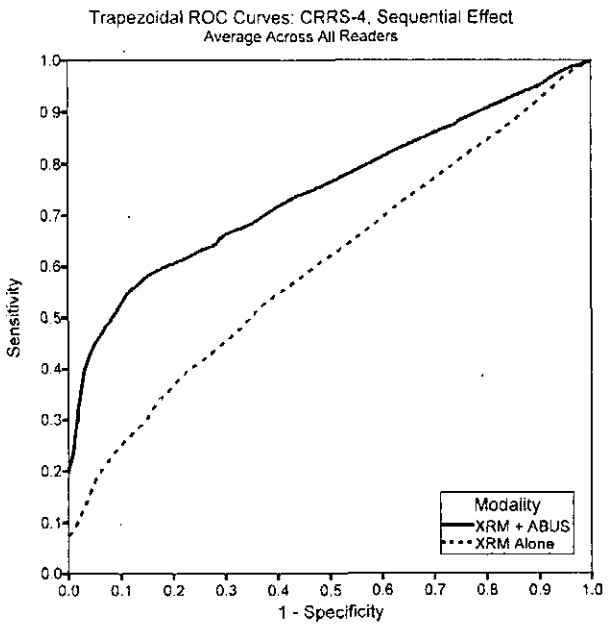

Figure 4. The overall ROC curves averaged across all readers trapezoidal ROC curves.

In the primary analysis, AUC was calculated empirically (trapezoidal method). Standard errors for the overall AUC values were calculated using the Dorfman-Berbaum-Metz (DBM) ANOVA-after-jacknife method. The corresponding overall AUC values are summarized in the Table 8, below.

Table 8. AUC estimates averaged across all readers

Comparison	AUC	Standard Error*	95% CI	P-value
$AUC_{XRM\ Alone}$	0.604	0.034	(0.536, 0.672)	
$AUC_{XRM+ABUS}$	0.747	0.037	(0.671, 0.822)	
$AUC_{XRM+ABUS} - AUC_{XRM\ Alone}$	0.143	0.035	(0.074, 0.212)	<.001

* Standard error derived from the DBM ANOVA-after-jackknife method.

Difference in AUC per reader

A scatter plot of reader-specific $AUC_{XRM+ABUS}$ vs. $AUC_{XRM\ Alone}$ demonstrating the

sequential effect by reader is shown below (Figure 5).

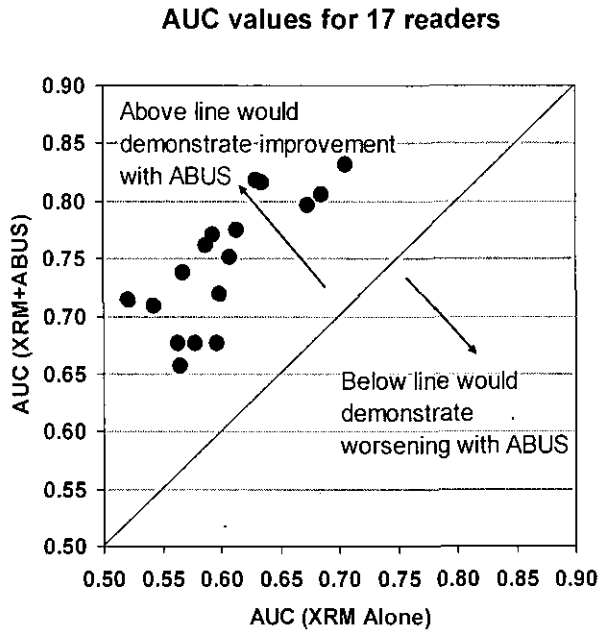

Figure 5. Area Under the Curve for 17 readers in the pivotal study.

Figure 6, below, shows the difference (black dots) in AUC (XRM+ABUS vs. XRM Alone) with corresponding 95% confidence interval by reader (horizontal lines).

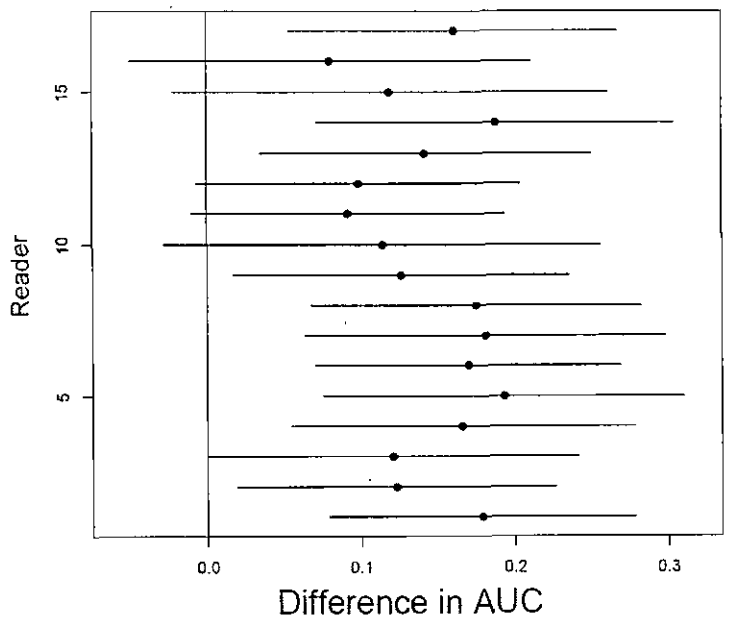

Figure 6. Difference in Area Under the Curve with 95% confidence interval for each of the 17 readers in the pivotal study.

Secondary Analysis: Sensitivity and Specificity

The sponsor provided the averaged and reader-specific descriptive summaries of

sensitivity and specificity at the case level and at the location level.

The averaged estimates of sensitivity and specificity at the case level are shown in the Table 9, below. Also, sensitivity presented at the location level is shown. All numbers, except for the sample sizes (N), are percentages. Point estimates and 95% confidence intervals were derived by the bootstrap method.

Table 9. Averaged estimates of sensitivity and specificity

	N	Cutoff Threshold =BIRADS 3			Cutoff Threshold =BIRADS 4a		
		XRM Alone	XRM+ ABUS	Difference (95% CI)	XRM Alone	XRM+ ABUS	Difference (95% CI)
Location-sensitivity	31	23.0	51.6	28.4 (16.5, 41.8)	18.8	49.9	30.9 (19.4, 43.8)
Case sensitivity	31	38.5	62.4	23.7 (10.0, 37.9)	27.1	57.7	30.6 (18.1, 43.0)
Case specificity	133	78.1	76.2	-2.1 (-8.0, 3.8)	88.0	84.0	-4.2 (-9.3, 0.4)

At a cut point of 3, where cases are considered to be recalled with BI-RADS ratings of 3 or higher:

- ABUS read sequentially with XRM provided an increase in sensitivity of 23.7 (95% CI: 10.0%, 37.9%). The overall sensitivity across all readers was 38.5% for XRM alone and 62.4% for XRM+ABUS.
- ABUS read sequentially with XRM provided an overall specificity across all Readers of 78.1% for XRM alone and 76.2% for XRM+ABUS, yielding a change in specificity of -2.1% (95% CI: -8.0%, 3.8%).

At a cut point of 4, where cases are considered to be recalled with BI-RADS ratings of 4 or higher:

- ABUS read sequentially with XRM provided an increase in sensitivity of 31.0 (95% CI: 18.7%, 43.9%). The overall sensitivity across all readers was 27.1% for XRM alone and 57.7% for XRM+ABUS.
- ABUS read sequentially with XRM provided an overall specificity across all Readers of 88% for XRM alone and 84% for XRM+ABUS, yielding a change in specificity of -4.2% (95% CI: -9.3%, 0.4%).

Change in sensitivity and specificity per reader

Figures 7 and 8, below, show how readers in the study changed their operating point (one line per reader): (Figure 7) BIRADS=3, and (Figure 8) BIRADS=4a as the cutpoints, respectively. Each line connects (sensitivity, specificity) pairs per reader. The unfilled circle of each line indicates reader sensitivity and specificity without ABUS; the filled circle indicates reader sensitivity and specificity with ABUS. The heavy black line above the diagonal line illustrates the average change in sensitivity and specificity.

The x-axis is 1 – specificity, so that moving from right to left represents an improvement in specificity (e.g. see the pink line). The y-axis is sensitivity, so that moving from south

to north represents an improvement in sensitivity (e.g. see the heavy black line).

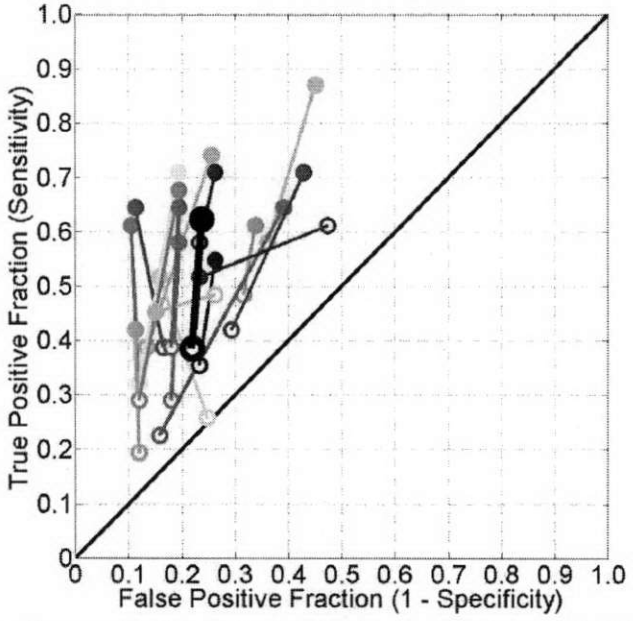

Figure 7. Change in sensitivity and specificity by reader, with BIRADS=3 as the cutpoint. Heavy black line shows the average change. Each filled and unfilled circle indicates estimates with and without ABUS respectively.

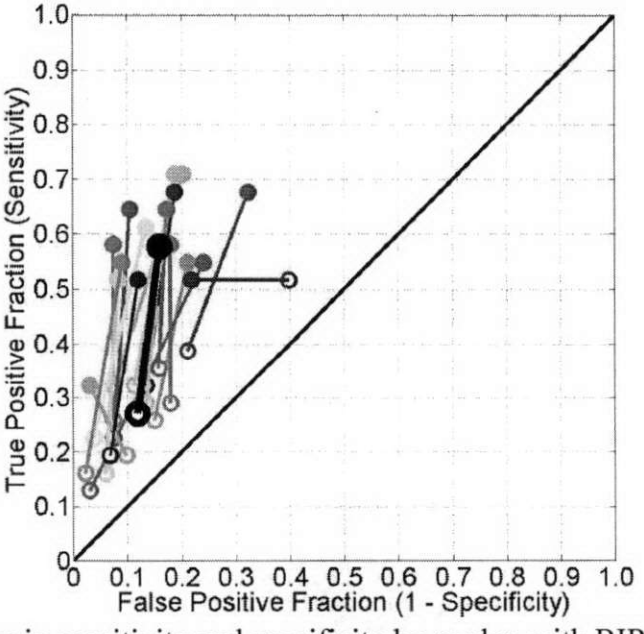

Figure 8. Change in sensitivity and specificity by reader, with BIRADS=4a as the cutpoint. Heavy black line shows the average change. Each filled and unfilled circle indicates estimates with and without ABUS respectively.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

It is noted that the selection criteria (Section X.A.1) differed for cancer and non-cancer subjects.

Specifically non-cancer subjects were excluded if the patient had prior breast interventional procedures. However, there was 1 non-cancer patient with prior breast intervention. In contrast, cancer subjects were excluded only if a prior breast intervention had occurred within one year prior to examination. It is noted that 15 of 31 (48%) cancer subjects had prior breast interventions more than 1 year prior to examination.

Non-cancer patients with prior breast interventions were not studied (except one). And Cancer patients with prior breast interventions were in the study.

Note that the estimates of the area under the ROC curve (AUC), sensitivity and specificity provided above were obtained from a population of patients with and without prior breast interventions (PBI). However the Indications for Use (IFU) indicate that the intended use population is composed of women without prior breast interventions. In order to address the limitation of having different selection criteria for cancer and non-cancer patients, and to align the study population with the intended use population in the Indications for Use (IFU), a revised analysis was subsequently conducted on the Cancer cases and Non-Cancer cases that had no prior clinical breast interventions. Therefore, estimates of AUC, sensitivity and specificity based on the study population that excludes patients with prior breast interventions are presented next.

Area under the ROC curve (AUC) excluding subjects with PBI

An AUC analysis that excludes 15 cancer patients and 1 non-cancer patient with prior breast interventions provides the following estimates using the Dorfman-Berbaum-Metz (DBM) approach (Table 10).

Table 10: Reader averaged AUC estimates, excluding subjects with prior breast interventions

	XRM	XRM+ABUS	Difference
AUC	0.566	0.782	0.215
(95% CI)	(0.472,0.662)	(0.676,0.888)	(0.101,0.330)

ABUS read sequentially with XRM provided a statistical significant increase in reader-averaged area under the ROC curve (AUC) of 0.215 (95% CI: 0.101, 0.330). The reader-averaged AUC was 0.566 (95% CI: 0.472, 0.662) for XRM alone and 0.782 (95% CI: 0.676, 0.888) for XRM+ABUS.

The overall ROC curves averaged across all readers' trapezoidal ROC curves are shown in Figure 9. For the trapezoidal curves, the sensitivity was averaged for every interval of 0.01 on the x-axis.

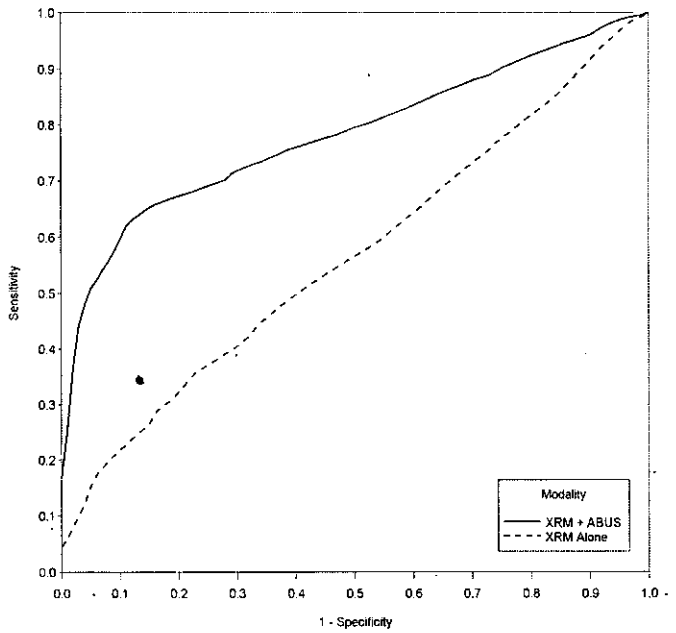

Figure 9. The overall ROC curves averaged across all readers trapezoidal ROC curves.

Difference in AUC per reader (excluding subjects with PBI)

Figure 10, below, shows the difference (black dots) in AUC (XRM+ABUS vs. XRM Alone) with corresponding 95% confidence interval by reader (horizontal lines), excluding subjects with prior breast interventions.

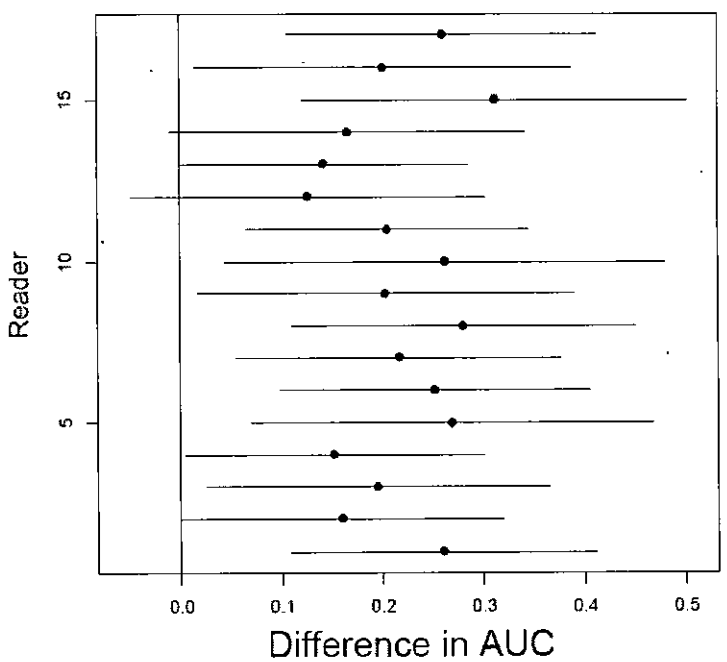

Figure 10. Difference in AUC and 95% confidence interval for each of the 17 readers in the pivotal study, excluding subjects with prior breast interventions.

Sensitivity and Specificity (excluding subjects with PBI)

Averaged estimates of sensitivity and specificity excluding subjects with prior breast interventions are provided in Table 11. All numbers, except for the sample sizes (N), are percentages. Point estimates and 95% confidence intervals were derived using the bootstrap method.

Table 11. Averaged estimates of sensitivity and specificity without prior breast interventions

	N	Cutoff Threshold =BIRADS 3			Cutoff Threshold =BIRADS 4a		
		XRM Alone	XRM+ ABUS	Difference (95% CI)*	XRM Alone	XRM+ ABUS	Difference (95% CI)*
Location Sensitivity	16	15.0	56.5	41.5 (21.5, 61.9)	13.1	55.4	42.3 (23.0, 61.6)
Case sensitivity	16	32.4	68.1	35.7 (17.8, 54.0)	22.1	64.2	42.1 (24.8, 59.7)
Case specificity	132	78.1	76.01	-2.0 (-7.9, 3.9)	88.1	83.9	-4.2 (-8.9, 0.8)

* 95% Confidence intervals were obtained using a bootstrap methodology considering readers and cases as random. 1000 bootstrap replicate samples were used.

At a cut point of 3, where cases are considered to be recalled with BI-RADS ratings of 3 or higher:

- ABUS read sequentially with XRM provided a statistically significant increase in sensitivity of 35.7% (95% CI: 17.8%, 54.0%). The averaged sensitivity across all readers was 32.4% for XRM alone and 68.1% for XRM+ABUS.
- ABUS read sequentially with XRM provided an averaged specificity across all Readers of 78.1% for XRM alone and 76.1% for XRM+ABUS, yielding a non-statistically significant change in specificity of -2.0% (95% CI: -7.9%, 3.9%).

At a cut point of 4, where cases are considered to be recalled with BI-RADS ratings of 4 or higher:

- ABUS read sequentially with XRM provided a statistically significant increase in sensitivity of 42.1% (95% CI: 24.8%, 59.7%). The averaged sensitivity across all readers was 22.1% for XRM alone and 64.2% for XRM+ABUS.
- ABUS read sequentially with XRM provided an averaged specificity across all Readers of 88.1% for XRM alone and 83.9% for XRM+ABUS, yielding a non-statistically significant change in specificity of -4.2% (95% CI: -8.9%, 0.8%).

Change in sensitivity and specificity per reader (excluding subjects with previous clinical breast intervention)

In the study population that excludes subjects with prior breast interventions, figures 11 and 12, below, show how readers in the study changed their operating point (one line per reader): (Figure 11) BIRADS=3, and (Figure 12) BIRADS=4a as the cutpoints, respectively. Each line connects (sensitivity, specificity) pairs per reader. The unfilled circle of each line indicates reader sensitivity and specificity without ABUS; the filled circle indicates reader sensitivity and specificity with ABUS. The heavy black line above the diagonal line illustrates the average change in sensitivity and specificity.

The x-axis is "1 – specificity", so that moving from right to left represents an improvement in specificity. The y-axis is sensitivity, so that moving from south to north represents an improvement in sensitivity.

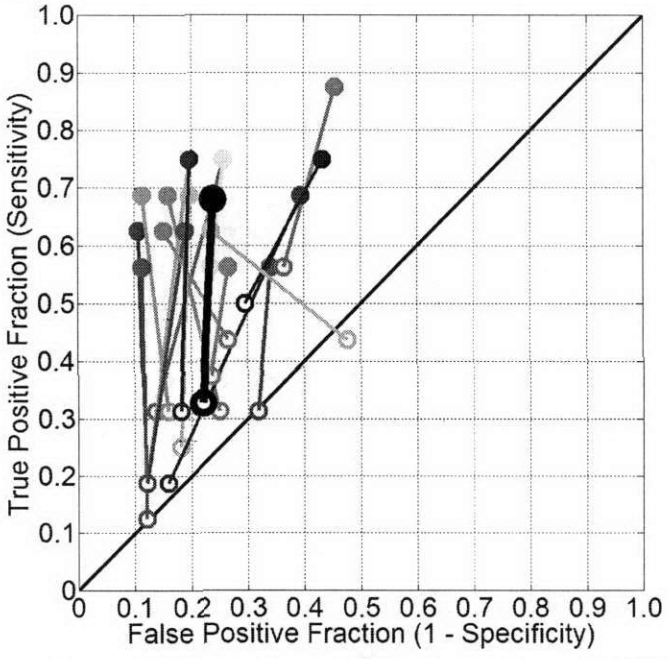

Figure 11. Change in sensitivity and specificity by reader, with BIRADS=3 as the cutpoint, excluding subjects with previous clinical breast intervention. Heavy black line shows the average change. Each filled and unfilled circle indicates estimates with and without ABUS respectively.

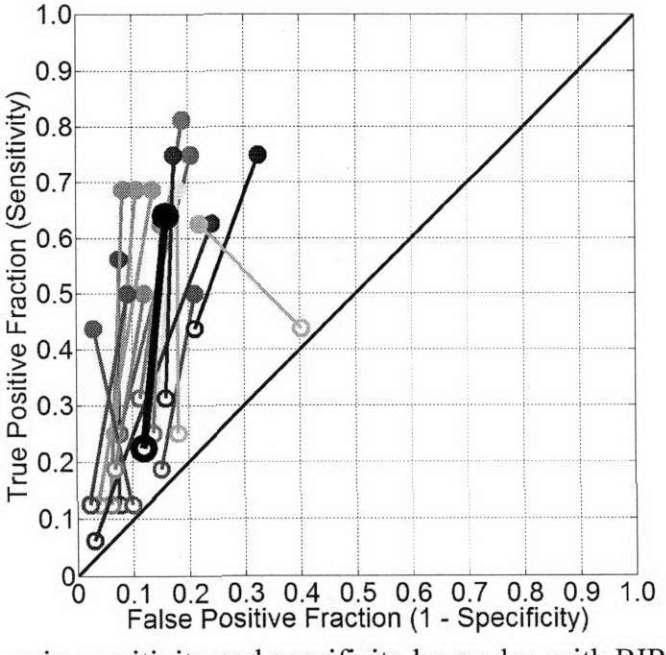

Figure 12. Change in sensitivity and specificity by reader, with BIRADS=4a as the cutpoint, excluding subjects with previous clinical breast intervention. Heavy black line

shows the average change. Each filled and unfilled circle indicates estimates with and without ABUS respectively.

Additional Analyses

As of June 3, 2011, 60 of 133 (45%) normal subjects in class 5 in the CRRS-4 study, had not confirmed completion of follow-up and true cancer status due to one of the following reasons: 1) subject had completed follow-up, but the data had not yet been entered into the database by the clinical site study staff or 2) Subject had not yet completed follow-up. As of December 7, 2011, 37 of the 60 subjects have completed follow-up and 23 of 133 (17%) normal subjects have not confirmed completion of follow-up and true cancer status.

Analyses of robustness to the missing verification of true disease status were conducted. In summary, in these analyses either 1, 2 or 3 of the 23 not-followed unverified cases were randomly selected and considered to be cancer cases using a bootstrap procedure. Based on this analysis, up to three false negative cases (false normal cases) do not result in any material effect on conclusions for the analysis in AUC.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

At an advisory meeting held on April 11, 2012, the Radiology Advisory Panel voted 13-0-0 (yes, no, abstain) that there is reasonable assurance the device is safe, 13-0-0 (yes, no, abstain) that there is reasonable assurance that the device is effective, and 13-0-0 (yes, no, abstain) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

Panel transcripts can be found at the following link:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/ucm299053.htm

XIII. CONCLUSIONS DRAWN FROM CLINICAL RETROSPECTIVE READER STUDY

The data from the pivotal study demonstrates that use of the U-Systems somo·v® Automated Breast Ultrasound System (ABUS) in conjunction with mammography provides a statistically-significant improvement in a Reader's ability to detect mammography-negative breast cancers in women with >50% parenchymal breast density, as compared to mammography alone, with no statistically-significant reduction in specificity.

A. Effectiveness Conclusions

The results obtained from the pivotal study demonstrate the effectiveness of the ABUS device in detecting a number of cancers in a sub-population of dense-breasted women who have had a negative mammogram. The effectiveness of the device was not completely evaluated for women who have had prior breast interventions. Furthermore, the pivotal studies were conducted in an environment where the ABUS images were read concurrently with the patient's mammogram. Therefore, physicians should be advised that the ABUS images should be interpreted in conjunction with the patient's mammograms.

B. Safety Conclusions

Ultrasound imaging has a very low risk profile for both the patient and the operator. There are no safety concerns for the ABUS device.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in the non-pivotal and pivotal clinical studies conducted to support the PMA approval as described above. The primary benefit of the ABUS system is improved sensitivity for detection of breast cancer in a group of women at higher risk for cancer and in whom mammography has been demonstrated to be less effective. Additional benefits of the device include non-ionizing radiation that do not carry the potential harmful effect of X-rays, painless examinations with no significant compression of the breast, open scanning environment that does not cause claustrophobic feelings. Furthermore, the ABUS examination is rapid, taking on average about 1 minute for scanning, and 15 minutes total with patient setup.

The objective of ABUS is non-invasive ultrasound examination of breast tissue to identify breast tumors that are occult to both mammography and physical examination. This is a clear benefit to patients with dense breast tissue, providing critical lead time in the early diagnosis of breast cancers that would otherwise be missed by mammography. Early detection is crucial to patient prognosis because breast cancer is not a systemic disease at its onset; it is a progressive disease, which can be arrested if treatment is initiated when tumors are small. Smaller tumors require less radical treatment and patients diagnosed with early stage cancers are more likely to survive [3, 4]. The ABUS System, when used for breast cancer screening as an adjunct to mammography, can bridge the early detection gap for women with dense breast tissue. It is concluded that the benefits of ABUS outweigh the potential risks.

The duration of the benefit for most women who undergo ABUS examination, and have a negative result, is one year, i.e. till the next screening examination. For patients with true-positive test results, for whom timely detection by the device might make the difference between early death and long-term survival, the duration of the benefit will be lifelong. Both benefits are of extreme value to potential cancer patients who are fearful for their lives.

Probable risks of the ABUS device are in terms of diagnostic accuracy, i.e. false positive and false negatives. A false positive test would lead to additional imaging evaluation that would otherwise not be performed. The additional workup most likely would be diagnostic ultrasound, which is another painless test. If further evaluation confirmed an abnormality or found another unrelated abnormality, biopsies may be performed. The additional workup would result in increased expense for the patient and a small risk of additional discomfort and complications such as infection if a biopsy were performed. The risk of a serious complication is extremely low. The consequences of a false negative would be a delay in diagnosis; however, this delay would happen for certain if the ABUS device were not used.

It is expected that thorough appropriate training a decrease in the rate of false positives could be achieved. Experience and progressive improvement of ultrasound imaging technology is

expected to result in a decrease of the risk of false positives and will additionally reduce the risk of further workup resulting in a benign lesion biopsy.

The patients having additional workup may experience anxiety during the workup but, as suggested by testimony at the 11 April Panel meeting and multiple web sites, this anxiety is preferable to the false sense of security given by a negative mammogram report in a dense breasted woman when in fact mammogram is quite insensitive for cancer detection in that patient population. In fact, while a small percentage of patients might experience some increased anxiety during the workup of lesions discovered by the ABUS system, lessened anxiety and increased peace of mind would be achieved in the much larger group of women at higher risk for cancer who would have the comfort of knowing that a more reliable cancer detection method (mammography plus the ABUS) has shown a negative result.

In conclusion, given the available information above, the data support that for the intended use of the device the probable benefits outweigh the probable risks. The discussions of the Radiology Advisory Panel expressed the clinical need for cancer screening in dense-breasted women, a benefit offered by the ABUS device. In their deliberations, the Panel discussed the probable risks that are presented above, i.e. false positive and false negative rate. The Panel also discussed that the ABUS device would represent an additional step in the clinical diagnostic workup for the intended population. The Panel members considered that a general scientific study of the performance of the device, exploring the false positive rate of the device, could provide valuable information for the general understanding of device performance. However, no post-market studies were recommended. The overall conclusion of the deliberations aligned with the evaluation of the FDA review team that the probable benefits outweigh the probable risks of the ABUS device.

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. The results of the Pivotal studies demonstrate that the ABUS device is safe and effective for breast cancer screening in asymptomatic women for whom screening mammography findings are negative or benign (BI-RADS Assessment Category 1 or 2), with dense breast parenchyma (BI-RADS Composition/Density 3 or 4), and have not had previous clinical breast intervention. Furthermore, there is reasonable assurance that the benefits outweigh the risk.

XIV. CDRH DECISION

CDRH issued an approval order on September 18, 2012. The final conditions of approval are cited in the approval order.

The applicant's manufacturing facility was 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

1. Pisano et al, Diagnostic Performance of Digital versus Film Mammography for Breast Cancer Screening, New England Journal of Medicine 2005; 353: 1773-1783.
2. Boyd et al, Mammographic Density and the Risk and Detection of Breast Cancer, New England Journal of Medicine; 2007; 356: 227-236.
3. Roubidoux et al, Invasive Cancers Detected After Breast Cancer Screening Yielded a Negative Result: Relationship of Mammographic Density to Tumor Prognostic Factors, Radiology 2004, Vol. 230: 42-48.
4. Tabár, Tot, Dean. Breast Cancer, the Art and Science of Early Detection with Mammography. The Impact of Early Detection on Breast Cancer Death, 2005, pg. 187.