SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Digital Breast Tomosynthesis

Device Trade Name: SenoClaire

Device Procode: OTE

Applicant's Name and Address: GE Healthcare
3000 N. Grandview Blvd.
Waukesha, WI 53188

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130020

Date of FDA Notice of Approval: August 26, 2014

Priority Review: Not Applicable

II. INDICATIONS FOR USE

SenoClaire acquires 2D images and also acquires multiple projection views to produce 3D DBT images suitable for screening and diagnosis of breast cancer. The SenoClaire option can be used for the same clinical applications as traditional mammography for screening mammography.

A screening examination will consist of:

- A 2D image set consisting of a craniocaudal view and of a mediolateral oblique view, or
- A 2D craniocaudal view and 3D mediolateral oblique image set.

The SenoClaire Digital Breast Tomosynthesis (DBT) option to Senographe Essential FFDM system may also be used for additional diagnostic workup of the breast.

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SenoClaire labeling.

V. DEVICE DESCRIPTION

SenoClaire consists of an add-on breast positioning device, a reconstruction computer and a firmware/software upgrade for the Senographe Essential FFDM system (already approved via P990066/S024). It enables the acquisition of both 2D digital mammograms and Digital Breast Tomosynthesis (DBT) images that can be used for screening or diagnostic mammography.

SenoClaire's motorized breast positioning device, the Motorized Tomosynthesis Device (MTD), is mounted onto the Senographe Essential in lieu of the bucky. When in place, it enables the acquisition of 9 low dose exposures using a "step-and-shoot" mode over a 25° arc. The set of projections is used to reconstruct a series of thin planes parallel to the detector through the breast volume, called Digital Breast Tomosynthesis images. The system also generates "slabs" which are projections of multiple planes onto the same image to produce a desired thickness of tomographic data. Screening 2D views and some diagnostic 2D views can be acquired with the MTD in place.

As needed, the MTD can be added or removed by the technologist. The Senographe Essential system retains all its existing clinical applications once the MTD is removed.

SenoClaire produces 2D and DBT DICOM datasets for display and archive on compatible mammography DICOM devices.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for breast cancer screening and diagnosis. These include clinical breast examination, film-screen mammography, digital mammography; contrast enhanced spectral mammography, ultrasound, and magnetic resonance imaging. The Hologic Selenia Dimensions 3D System, approved by FDA via PMA P080003, can also produce DBT images.

After detection of an abnormality, a biopsy and pathologic examination may be performed to diagnose the cancer. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The SenoClaire option was CE marked in June, 2013. It is commercially available in the following countries: Algeria, Argentina, Austria, Australia, Bangladesh, Belarus, Belgium, Bulgaria, Canada, Chile, Czech Republic, Denmark, Egypt, France, Germany, Great Britain, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Malaysia, Mexico, Netherlands, New Zealand, Norway, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, Venezuela, Vietnam.

SenoClaire has not been withdrawn from any market for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of SenoClaire. These potential adverse effects are common to all mammography systems:

- Excessive breast compression
- Excessive x-ray exposure
- Electrical shock
- Skin irritation, abrasion, or puncture wound
- Infection

Two minor adverse events and no serious adverse event were reported for the patients enrolled in the clinical study. For the specific adverse events that occurred in the clinical study, please see Section X below.

Failure of the device to perform as expected or failure to correctly interpret the images produced by the device may lead to improper patient management decisions. False positives would lead to additional exams that would result in a small risk of additional discomfort and complications such as infection or bleeding if a biopsy were performed. The risk of a serious complication is extremely low. False negatives would not be recalled which may result in delay in diagnosis and progression of disease up until the next screening exam.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Bench Testing

Where applicable to a digital breast tomosynthesis system, the sponsor followed the physical laboratory testing methods mentioned in the FDA guidance for Class II Full-Field Digital Mammography (FFDM) system. Some of the testing conducted involved new measurements important to DBT although they are not currently included in standards or advised by guidance.

Table 1: Bench Testing and Sample Image Evaluation

Test	Purpose	Acceptance Criteria	Results
Bench tests specific to the DBT mode			
Apparent source size	Measure the apparent increase in source size resulting from the multiple exposures with moving source.	Change in apparent source size and focal spot should be clinically negligible.	Apparent blurring: 54 µm, no impact on clinical images.

Apparent focal spot size and effect of angle inaccuracy	Assess the effect of source motion and vibrations on the apparent focal spot size.	Focal spot size should be comparable to conventional 2D imaging to ensure detectability of small objects.	Potential impact on MTF at 3 lp/mm is less than 5%. "Step-and-shoot" acquisition preserves the focal spot size. Angle inaccuracies are negligible.
Artifact Spread Function: Impulse response along the z-axis	Assessment of out-of-plane artifacts.	Visual assessment of the reduction in out of plane artifacts	Out of plane artifacts are effectively reduced.
Image Uniformity: - Signal non-uniformity and SNR non-uniformity on a flat field phantom. - Resolution uniformity measured on a mesh.	Characterization of reconstructed image uniformity in and across the reconstructed DBT planes. Comparison of the case acquisition prototype and final device.	System characterization – No pass/fail criteria	Signal non-uniformity is less than 2% over 95% of the 2D field-of-view; less than 18% overall. SNR non-uniformity is less than 24% overall. Resolution non-uniformity is less than 20%.
Bench tests using methods described in the FDA Class II Special Controls Guidance Document for Full Field Digital Mammography System			
Modulation Transfer Function (MTF)	Quantitative measure of the spatial resolution properties of the image acquisition system. Assessment of angular exposure to MTF	System Characterization – No pass/fail criteria	MTF curve perpendicular to detector and at larger angles which give worse MTFs.
Noise Power Spectrum (NPS)	Quantitative measure of the noise properties of the image acquisition system	System Characterization – No pass/fail criteria	Noise level inferior in the final device than in the case accrual device
Detective Quantum Efficiency (DQE)	Quantitative measure of the efficiency of signal-to-noise ratio (SNR) transfer of the image acquisition system Comparison between the prototype used in	System Characterization – No pass/fail criteria	The DQE in the low-frequency range remains within 15% of its maximum (high-dose) value, while the DQE at higher frequencies drops to about 50%

	the accrual study and the final device		its maximum value in the lowest dose range.
Dynamic Range	Quantitative measure of the dynamic range of the image acquisition system	Linearity of detector response	All R values are above 0.9994, indicating excellent linearity over the measurable detector dose interval.
Average Glandular Dose on PMMA plates.	Comparison of radiation dose delivered in DBT mode and in FFDM mode with Automatic Exposure Control for variable breast thickness	Radiation dose comparable to FFDM across a clinically relevant range of thickness	The average glandular dose delivered in DBT mode matches that delivered in FFDM for breast thickness ranging between 2 and 7 cm.
Image erasure and fading: repeated exposure test	Assessment of effects of on successive projections in an imaging sequence and in consecutive imaging sequences.	The measured residual signal should be negligible compared to the next acquisition.	Measured average residual signal from one projection to another is less than 0.6% and less than 0.0004% for one imaging sequence to the next. Impact of ghosting is negligible.
ACR Mammography Accreditation Phantom Images	Detectability of small structures in the breast	MQSA minimum requirement	Images quality sufficient to meet the minimum ACR accreditation requirement
Sample Clinical images	Visual image quality assessment	Images deemed of clinical quality by a board certified and MQSA qualified radiologist	Sample images were found to be of acceptable quality for clinical use

B. <u>Additional Studies</u>

The sponsor provided certificate of conformance to the following standards:

- IEC 60601 Medical electrical equipment
  - Part 1-1: General requirements for basic safety and essential performance,
  - Part 1-3: General requirements for radiation protection in diagnostic X-ray equipment.
  - Part 1-4: Programmable Electrical Medical Systems
  - Part 1-6: Usability

- Part 2-32: Particular requirements for the safety of X-ray equipment
- Part 2-45: Particular requirements for the safety of mammographic X-ray equipment and mammographic stereotactic devices.

- IEC 62366: Application of usability engineering to medical devices.

GE Healthcare provided design and software testing documentation consistent with FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. The sponsor conducted software unit testing and integration testing used to verify that all the sub-systems satisfy the software requirements and integrate successfully. System testing was also conducted to validate that the software specifications conform to its intended use and user requirements. The sponsor conducted regression testing to ensure that new software features introduced by the tomosynthesis option do not create problems with previous version of the software. Impact analysis was also provided as a justification for test case selection in the regression testing. All the test activities were completed successfully.

1. Conclusion of Non-Clinical Testing

Bench testing and examination of sample clinical images demonstrates that the SenoClaire system can be used to produce diagnostic quality DBT images at a dose comparable to FFDM.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of SenoClaire for breast cancer screening and diagnosis in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Clinical Study	Study Design	Study Objective	Number of Sites/Readers	Number of Subjects
Accrual GE 190-001, -002, -003	Prospective subject accrual	Subject Accrual for blinded reader study Evaluate the safety of the device	6 enrollment sites	753 patients
Blinded Image Evaluation GE 190-004	Blinded reader study, partially randomized controlled clinical trial on an enriched case set	Evaluate the safety and effectiveness of the device Primary endpoints: Non-inferiority of DBT MLO, and DBT MLO + 2D CC to 2-view FFDM as measured by the area under the ROC Curve	7 readers	444 cases (67 cancers, 377 noncancers)

A. Case Acquisition Study

GE Healthcare designed and conducted a prospective clinical case acquisition study to collect traditional 2-view FFDM images and DBT images to be used for the pivotal reader study. Patients were enrolled between June 2007 and March 2010.

A total of 753 patients were enrolled from 5 United States clinical sites and 1 Canadian clinical site under 3 IRB approved clinical case acquisition protocols:

- GE 190-001 Screening cohort ("A Multicenter Study to Test the Non-Inferiority of Digital Breast Tomosynthesis Compared to Full-Field Digital Mammography in Detecting Breast Cancer. Part 1. Recruitment Plan for Asymptomatic Women Undergoing Screening Mammography"): Subjects enrolled under this protocol were asymptomatic and scheduled to undergo a routine screening mammogram at the time of consent.

- GE 190-002 Diagnostic cohort ("A Multicenter Study to Test the Non-Inferiority of Digital Breast Tomosynthesis Compared to Full-Field Digital Mammography in Detecting Breast Cancer. Part 2. Recruitment Plan for Asymptomatic Women Referred for Diagnostic Mammography"): Subjects enrolled under this protocol were asymptomatic patients referred for diagnostic imaging after a routine screening mammogram.

- GE 190-003 Biopsy cohort ("A Multicenter Study to Test the Non-Inferiority of Digital Breast Tomosynthesis Compared to Full-Field Digital Mammography in Detecting Breast Cancer. Part 3. Recruitment Plan for Asymptomatic Women Referred for Breast Biopsy"): Subjects enrolled under this protocol were asymptomatic women referred for breast biopsy after a routine screening mammogram and diagnostic workup.

In addition, some cases enrolled in separate clinical trials at the Massachusetts General Hospital and the University of Padua, Italy, were used for enrichment. The enrichment data included initially asymptomatic biopsy-confirmed cancer cases that met all other criteria of GE Healthcare's prospective studies.

All enrolled subjects had routine 2-view (MLO and CC) screening mammograms on a GE FFDM system before or upon enrollment. In addition subjects were imaged with a prototype mounted on a GE Senographe DS FFDM system with MLO positioning (DBT MLO).

The 2D FFDM images from screening mammography and/or diagnostic mammography and the DBT images were provided in digital format to the sponsor.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria

Enrollment in the Case Acquisition study was limited to patients who met the following inclusion criteria

- Women 18 years or older, presenting for screening mammography;
- Able and willing to comply with study procedures, and have signed and dated the informed consent form;
- The subject is either surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy), or postmenopausal (cessation of menses for more than 1 year); or, if of childbearing potential, the possibility of pregnancy is remote based on a negative patient history and, optionally, a negative urine pregnancy test (if subject requests one).

Exclusion Criteria

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

- Pregnant or trying to become pregnant;
- Have signs or symptoms of breast cancer;
- Have been previously included in this study;
- Have breast implants;
- Have a history of breast cancer and is in active treatment. However, subjects with a prior lumpectomy who receive only routine screening mammography views can be included. Additionally, subjects with prior mastectomy currently not being treated can be included in the screening imaging of the unaffected breast;
- Have undergone mammography for any purpose within approximately one year;
- Have breasts too large to be adequately positioned on 19 x 23 cm FFDM digital receptor without anatomical cut off during a DBT examination.

2. Follow-up Schedule

All subjects were asked to undergo a follow-up mammogram approximately 1 year after DBT examination with the exception of subjects who had either a histopathologically confirmed positive diagnosis of cancer in both breasts or a previous mastectomy with a histopathologically confirmed diagnosis of cancer in the remaining breast. These patients were not asked to return for the 1-year follow-up.

The 1-year follow-up or histopathology result determined the subject's final clinical diagnosis for the study. Subjects that had a negative mammogram at 1 year were classified as having a final diagnosis of "no cancer". Discovery of a cancer at any time up to and including the 1-year examination resulted in the subject being assigned a final diagnosis of cancer.

B. Accountability of PMA Cohort

Table 2: Case Accrual Studies and Reader Study Patient Disposition

	GE 100-001	**GE 100-002**	**GE 100-003**	**Enrichment**	**Total**
Screened	419	241	107	n/a	767
Screen Failure	6	3	5	n/a	
Enrolled	**413**	**238**	**102**	**n/a**	**753**
Incomplete imaging: - adverse event - protocol violation - technical problem/machine malfunction - other	 1 3 14 2	 0 4 3 2	 9 6 0 0	n/a	
Cancers detected at enrollment (A)	**5**	**11**	**29**	**n/a**	**45**
Patients to be followed up after 1 year	388	218	58	n/a	664
Incomplete follow-up: - Lost to follow-up - Absence of follow up between 10-15 months - Other medical reasons	 30 49 9	 17 41 3	 5 13 0	n/a	
Patients that completed follow-up (B)	300	157	40	n/a	497
Cancer at the time of follow up	**3**	**4**	**4**	**n/a**	**11**
Patients eligible for BIE (A+B)	305	168	69	32	**574**
Patients enrolled in BIE (cancer, benign, normal)	304	82	84	12	482
Cases excluded from per-protocol analysis	9 normal cases due to technical problems	11 cases due to lack of truth	17 cases due to lack of truth	1 case due to lack of truth	38
Patients included in the per-protocol analysis (cancer, benign, normal)	295 (8, 7, 280)	71 (15, 15, 41)	67 (33, 34, 0)	11 (11, 0 ,0)	**444** **(67, 56, 321)**

At the time of randomization 610 subjects were available from the GE-190-001, -002, -003 and enrichment cohorts. The normal and benign cases were selected for the Blinded Image Evaluation (BIE) prior to completion of all of the 1-year follow-ups that confirmed a non-cancer truth status. Therefore in order to achieve the necessary 450 evaluable subjects, 482 subjects were randomly selected from the 610 available subjects available at the time to allow for a 10% loss. Similarly, cancer cases were over-sampled by 10% to allow for loss of eligible cases due to inadequate image quality as ascertained by BIE study readers.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a mammography study performed in the US (cf. Table 3).

Of the 67 malignant cases, two cases had cancer in both breasts. The malignant cases were fairly equally represented as invasive ductal carcinoma (IDC), ductal carcinoma in-situ (DCIS) and IDC+DCIS. A small proportion of the malignancies were invasive lobular carcinoma (ILC). Most (72%) of the malignancies were located in the upper quadrants. About one third of the malignancies were less than 1 cm in size (cf. Table 4).

Table 3: Demographic and Breast Density Distribution

Variable		Cancer cases (N=67)	Benign Cases (N=56)	Normal Cases (N=321)	All Cases (N=444)
Age	Mean	59.1	56.5	56.8	57.1
	Standard Deviation (SD)	10.84	12.29	10.24	10.62
	Range (min-max)	40-85	36-87	30-81	30-87
	<50 years	23.9%	39.1%	27.1%	27.5%
	>= 50 years	76.1%	66.1%	72.9%	72.5%
Breast Density	Almost entirely fat	6.0%	8.9%	13.1%	11.5%
	Scattered fibroglandular	44.8%	35.7%	40.8%	40.8%
	Heterogeneously dense	46.3%	50.0%	37.7%	40.5%
	Extremely dense	3.0%	5.4%	8.4%	7.2%

Table 4: Characteristics of cancer cases (n=67)

Type of cancer (two cases with different cancers in each breast)	# (%) IDC # (%) DCIS # (%) IDC+DCIS # (%) ILC	19 (28.4%) 26 (38.8%) 19 (28.4%) 5 (7.5%)
Location (some cases counted	# (%) Upper	48 (71.6%)

in multiple categories)	# (%) Lateral # (%) Medial # (%) Lower # (%) Outer # (%) Subareolar # (%) Other	26 (38.8%) 10 (14.9%) 9 (13.0%) 9 (13.0%) 6 (9.0%) 10 (14.9%)
Lesion Size	# (%) < 1cm # (%) ≥ 1 cm	24 (35.8%) 43 (64.2%)
Lesion Type	# (%) masses # (%) microcalcifications # (%) architectural distortions	31 (40.3%) 37 (48.1%) 9 (11.6%)

IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in situ; ILC: Invasive Lobular Carcinoma

D. Reader Study Design and Methods

GE Healthcare conducted a multi-case multi-reader (MRMC) study using an enriched subset of cases accrued in the prospective case acquisition studies. The objective was to demonstrate the non-inferiority of DBT to that of 2-view FFDM for the screening and diagnosis of breast cancer. The sponsor compared two different screening scenarios to 2-view FFDM in its study: DBT in MLO orientation only (DBT MLO) and DBT in MLO orientation plus a 2D view in CC orientation (DBT MLO + 2D CC).

1. Reference standards

The following criteria were used to categorize cases entered in the MRMC study.

All subjects were be asked to undergo a follow-up mammogram approximately 1 year after DBT examination with the exception of subjects who had either a histopathologically confirmed positive diagnosis of cancer in both breasts or a previous mastectomy with a histopathologically confirmed diagnosis of cancer in the remaining breast. These patients were not asked to return for the 1-year follow-up.

The 1-year follow-up or histopathology result determined the subject's final clinical diagnosis for the study. Subjects that had a negative mammogram at 1 year were classified as having a final diagnosis of "no cancer". Discovery of a cancer at any time up to and including the 1-year examination resulted in the subject being assigned a final diagnosis of cancer.

If a case initially negative was found to be positive at the 1 year follow-up it is considered a positive case.

2. Readers

7 readers with significant breast imaging clinical experience participated in the study. Readers were board certified and MQSA qualified. Readers received 8 hours hands-on training with DBT using about 100 cases collected at the Massachusetts General Hospital.

Cases including masses, microcalcifications, and architectural distortions were reviewed in softcopy with the workstation to be used for the study. None of the cases included for training were used in the pivotal MRMC study.

3. Image Scoring

The study used a fully crossed design in which all readers reviewed all cases under three reading protocols:

- Arm 1: 2-view FFDM image sets consisting of bilateral CC and MLO images of each subject,

- Arm 2: DBT MLO image sets consisting of planar tomographic reconstructed image sets. Planes (1mm apart) and slabs (10 mm thick maximum intensity projections) over the full breast volume were available for review by the reader.

- Arm 3: DBT MLO + 2D CC including DBT MLO images along with 2D CC FFDM views of each breast.

Readers were blinded to the details of the patient histories. A cross-over design with a wash-out period of 4 weeks was employed. Cases were randomized into two groups that were read in a different modality in each of the three reading sessions (cf. Table 5). Cases within a group were further subdivided into five blocks. In a reading session, cases within a block were read consecutively but the order in which the blocks were read was randomized.

Table 5: Cross-Over Study Design – Modality for each reading session and each group

	Reading Session		
Group	1	2	3
1	FFDM	DBT MLO	DBT MLO + 2D CC
2	DBT MLO	FFDM	DBT MLO + 2D CC

The readers reported for each breast:

- A screening BI-RADS score (0, 1, 2);
- A restricted diagnostic BI-RADS score (1 through 5);
- A score of 1-7 on a suspicion of malignancy scale;
- Lesion characteristics for identified findings: location of lesion, type of lesion, view on which the lesion was visible if not on both, maximum lesion size;

In addition the reading time was monitored by the study organizer.

For each read of each case, the case based malignancy and BI-RADS scores were taken as:

- The most conservative (the highest) score of 2 cancer-free breasts or bilateral malignancies;

- In cases where a single breast has cancer, the score specific to the breast with cancer will be used;
- In cases where the subject has only 1 breast, the score of that single breast was used.

4. Receiver Operating Characteristic (ROC) Analysis

A multi-reader, multi-case (MRMC) ROC analysis using the malignancy score was used to compare ROC area under the curve (AUC) performance. Parametric and non-parametric ROC curves were calculated using the DBM (Dorfman-Berbaum-Metz [1]) MRMC (Multireader-Multicase) 2.32 build 3 Software ROC Analysis of Variance.

E. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 753 patients enrolled in the case acquisition study. There were two minor adverse events and no serious adverse event reported during the case acquisition study.

Adverse effects that occurred in the PMA clinical study:

Adverse events occurred in 2 subjects for an incidence rate of 0.3%. Both Adverse events occurred during DBT imaging and were mild and resolved.

One subject (randomized to be imaged with DBT first in the GE-190-001 study) reported pain in the left breast during the DBT procedure (before the compression paddle touched the breast) and asked to stop the study. Only one breast was imaged. The adverse event resolved upon stopping the procedure. Relationship to the imaging procedure was not suspected. The subject withdrew from the study.

One subject (GE-190-003 study) presented with a rash during DBT imaging and, due to this, the compression applied to the breast caused the skin to tear. This adverse event was non-serious but was suspected to be related to the DBT imaging. The nurse gave the subject Bacitracin zinc with polymoxin B sulfate ointment to prevent the tear from becoming infected. The adverse event was reported by the site as resolved.

2. Effectiveness Results: Primary Endpoints

The primary analysis for effectiveness evaluated whether the ROC AUCs for DBT MLO and DBT MLO + 2D CC were non-inferior to that of 2-view FFDM. The sponsor pre-specified a non-inferiority margin of 0.1. The FDA requested the analysis to be conducted with a non-inferiority margin of 0.05.

Table 6 summarizes the results of the ROC AUC comparison between the different reading protocols included in the study.

Table 6: ROC AUC analysis

	FFDM	DBT MLO	DBT MLO + FFDM CC
AUC value (standard error)	**0.853** (0.027) †	**0.820** (0.033) †	**0.842** (0.028) †
95% Confidence Interval on AUC	[0.798 , 0.908] †	[0.752 , 0.888] †	[0.786 , 0.899] †
DBT-FFDM difference in AUC (standard error)	n/a	-0.0331 (0.021) † -0.0356 (0.016) ‡	**-0.0107** (0.019) † -0.0097 (0.016) ‡
97.5% Confidence Interval on AUC difference – Bonferroni Correction for multiplicity testing	n/a	[-0.077, 0.010] † [-0.073, 0.002] ‡	**[-0.054 , 0.033]** † [-0.047 , 0.028] ‡

† Based on DBM (Dorfman-Berbaum-Metz) MRMC (Multireader-Multicase) 2.32 build 3 Software ROC Analysis of Variance - proper binormal ROC estimation

‡ Based on DBM (Dorfman-Berbaum-Metz) MRMC (Multireader-Multicase) 2.32 build 3 Software ROC Analysis of Variance - non-parametric ROC estimation

The mean difference in AUC ROC between DBT MLO and 2-view FFDM was -0.0331 (97.5% CI lower limit -0.073). The lower end of the 97.5% CI was larger than the sponsor-chosen non-inferiority criterion of -0.1 but lower than the FDA-specified non-inferiority criterion of -0.05.

The mean difference in AUC ROC between DBT MLO + 2D CC and 2-view FFDM was -0.0107 (97.5% CI lower limit: -0.054). The lower end of the 97.5% CI was larger than the sponsor chosen non-inferiority margin but slightly lower than the FDA-specified non-inferiority margin of -0.05. The non-parametric DBM analysis produced slightly smaller differences and a 97.5% CI lower limit of -0.047. FDA also performed confirmatory analyses using bootstrap resampling and OR method and found 97.5% CI lower limit slightly larger than -0.05 (cf. additional analyses in Table 8).

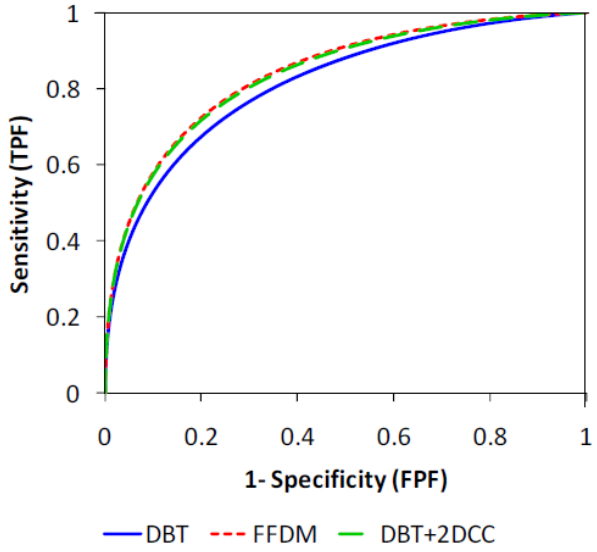

Figure 1: Average reader ROC of the three study arms.

Secondary endpoints included reader sensitivity, specificity and recall rate, as well as reading time and average glandular dose.

3. Effectiveness Results – Secondary Endpoints

Sensitivity is defined as the percentage of cancer cases whose screening BI-RADS was positive, i.e. category 0. Specificity is defined as the percentage of non-cancer cases whose screening BI-RADS was either negative or benign (category 1 or 2). The sponsor computed the individual recall rate defined as the percentage of cases with a screening BI-RADS score of 0. Table 7 summarizes the results of the secondary analyses.

Table 7: Secondary analyses (7 readers, 444 cases including 67 cancer cases and 377 non-cancer cases)

	FFDM	DBT MLO	DBT MLO + FFDM CC
Sensitivity (standard error)	0.831 (0.033)	0.750 (0.041)	0.786 (0.035)
95% CI on Sensitivity	0.767 , 0.896	0.669 , 0.831	0.717 , 0.854
Specificity (standard error)	0.671 (0.015)	0.724 (0.015)	0.736 (0.015)
95% CI on Specificity	0.641 , 0.701	0.694 , 0.754	0.707 , 0.766
Recall Rate (standard error)	0.406 (0.016)	0.348 (0.016)	0.340 (0.016)
95% CI on Recall Rate	0.374, 0.438	0.316, 0.380	0.308, 0.373

The secondary endpoints and were not accounted for in the multiple testing corrections, so the statistical significance of these findings cannot be assessed but the following was observed:

- Specificity based on screening BI-RADS was higher with DBT MLO + 2D CC than with 2-view FFDM.
- Recall rates based on screening BI-RADS were lower with DBT MLO + 2D CC than with 2-view FFDM.

The average radiation dose to subjects was identical for DBT MLO compared to 2-view FFDM used in the BIE, both 3.2 mGy per breast (standard error 0.07 for DBT MLO and 0.05 for 2-view FFDM).

On average, interpretation times were 41% longer with DBT MLO + 2D CC than with 2-view FFDM interpretations. This trend was consistent for malignant, benign and normal cases, with all modalities taking longer for malignant and benign cases than for normal cases.

4. Subgroup and Additional Analyses

Table 8: Summary of additional analyses

Additional Analysis	**Comments**
AUC ROC stratified per breast density, lesion type, lesion size and cancer type	The reader performance with DBT MLO + 2D CC as evaluated by ROC AUC does not show concerning trends in these subgroup analyses.
Effect of combining breast score to obtain a case based score on ROC AUC estimation	This analysis showed that the effect of combining breast based score to estimate a case based score does not significantly impact the ROC AUC results.
Correct localization of lesions (AUC AFROC analysis)	This analysis showed that the results are robust to enforcing that lesions be correctly localized by the reader in the BIE study.
Intent-to-diagnose analysis	This analysis showed that the study results are robust when including the 38 patients entered in the MRMC study lacking adequate follow-up information.
FDA bootstrap analysis [3] of ROC AUC differences between DBT MLO + 2D CC and 2-view FFDM	AUC_{FFDM} 0.829, 95% CI [0.776, 0.881] $AUC_{DBT\ MLO + 2D\ CC}$ 0.820, 95% CI [0.763, 0.877] $AUC_{DBT\ MLO + 2D\ CC}$ - AUC_{FFDM} -0.009, 97.5% CI: [-0.049, 0.030]
FDA Obuchowski-Rockette [4, 5] analysis of ROC AUC differences between DBT MLO + 2D CC and 2-view FFDM	AUC_{FFDM} 0.830, 95% CI [0.791, 0.869] $AUC_{DBT\ MLO + 2D\ CC}$ 0.821, 95% CI [0.775, 0.866] $AUC_{DBT\ MLO + 2D\ CC}$ - AUC_{FFDM}: -0.010, 97.5% CI: [-0.040, 0.021]
Mixed model in SAS with consideration of period, group carryover and modality carry-over effects for the estimation ROC AUC differences between DBT MLO + 2D CC arm and 2-view FFDM [2]	AUC_{FFDM}: 0.8401, 95% CI [0.7754, 0.9047] $AUC_{DBT\ MLO + 2D\ CC}$: 0.8299, 95% CI [0.7709, 0.8889] $AUC_{DBT\ MLO + 2D\ CC}$ - AUC_{FFDM}: -0.0102, 95% CI: [-0.616, 0.0412] with Dunnett–Hsu multiplicity correction

F. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 7 board certified and MQSA qualified radiologists. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiological Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Multi-Reader Multi-Case study showed that the difference in reader performance between DBT MLO + 2D CC and 2-view FFDM is on average -0.011 ROC AUC units with 97.5% CI [-0.055, 0.033]. While the lower limit of the 97.5% confidence interval is inferior to the -0.05 non-inferiority margin, the overall range of performance difference is clinically acceptable.

Combined with bench test results and sample image evaluation, the pivotal study results demonstrate that SenoClaire is non-inferior to 2-view FFDM when used according to its intended use.

B. Safety Conclusions

The risks of the device are based on bench testing as well as data collected in a clinical study conducted to support PMA approval as described above.

The risk of direct harm to the patient is minimal. There were two minor adverse events and no serious adverse event reported during the case acquisition study.

The risk of false positive and false negative clinical decisions based on the images produced by the proposed device is similar to that of 2-view FFDM for screening.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

SenoClaire is used to reconstruct the breast volume from limited angle projections while eliminating the tissue overlapping effect observed in 2D projections. It is likely to benefit a small number of screening patients whose cancers could have otherwise been missed due to tissue superimposition (false negatives), or who may otherwise have been unnecessarily referred for additional workup (false positives). While microcalcifications could be more difficult to visualize because of the thin slices, SenoClaire supports thick slab visualization which substantially overcomes this potential difficulty.

The proposed device has no significant risk of direct harm to the patient. The main risk of the device comes from the possibility of false positive and false negative clinical decisions when using the images produced by the SenoClaire. The sponsor conducted an MRMC study to compare the performance of readers with SenoClaire and with the standard of care 2-view FFDM. The study design is consistent with other mammography studies. Because MRMC studies are conducted outside of the clinical setting, with an enriched case set, and without patient history, the generalizability of some figures of merit such as recall rate, sensitivity and specificity is limited. The design is considered acceptable in order to reduce the size of the trial and avoid confounders.

Additional factors to be considered in determining probable risks and benefits for the SenoClaire device included some moderate design flaws in the reader study presented in this submission. The DBT MLO + 2D CC arm was initially planned as an exploratory arm and therefore not randomized into the reading schedule, nor accounted for in multiple testing correction methods. FDA conducted some additional analyses to assess the effect of not randomizing some of the reads and found that in this particular study the results were not likely to be affected. Confidence intervals were corrected using Bonferroni's multiplicity correction to account for the two study endpoints.

The set of evidence provided in the submission showed that the benefit/risk profile of SenoClaire is comparable to that of FFDM. In conclusion, given the available information described above, the data support that the probable benefits of breast cancer screening with SenoClaire by combining a DBT MLO and a 2D CC view outweigh the probable risks.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on August 26, 2014. There were no conditions of approval.

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

XIV. 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.

XV. REFERENCES

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