SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Cone Beam Breast Computed Tomography
Device Trade Name:	Koning Breast CT (Model CBCT 1000)
Device Procode:	OLQ
Applicant's Name and Address:	Koning Corporation 150 Lucius Gordon Drive Suite 112 West Henrietta, NY 14586
Date(s) of Panel Recommendation:	None.

Premarket Approval Application (PMA) Number: P130025

Date of FDA Notice of Approval:	January 14, 2015
Priority Review:	Not Applicable

II. INDICATIONS FOR USE

Koning Breast CT (CBCT1000) is a cone beam computed tomography system intended to provide three dimensional images for diagnostic imaging of the breast. Koning Breast CT should be read along with standard 2-view mammography (CC and MLO views).

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Koning Breast CT (CBCT1000) labeling.

V. DEVICE DESCRIPTION

The Koning Breast CT (KBCT) (model CBCT1000) is a dedicated breast imaging system utilizing cone beam breast CT technology to provide 3D isotropic volume images of the breast for breast cancer diagnosis. The KBCT is intended for diagnostic breast imaging in patients who have signs or symptoms of disease, or those who have abnormal imaging findings. It is not intended for breast cancer screening in an asymptomatic population. The KBCT consists of a horizontal CT gantry, an X-ray/data acquisition subsystem mounted on a rotation assembly, a patient table and an operator console with an image

processing sub-system, standard monitors (>1 MP) for modality control and image review at the operator's console and a 3D visualization/DICOM storage package. Photos of the system are provided below:

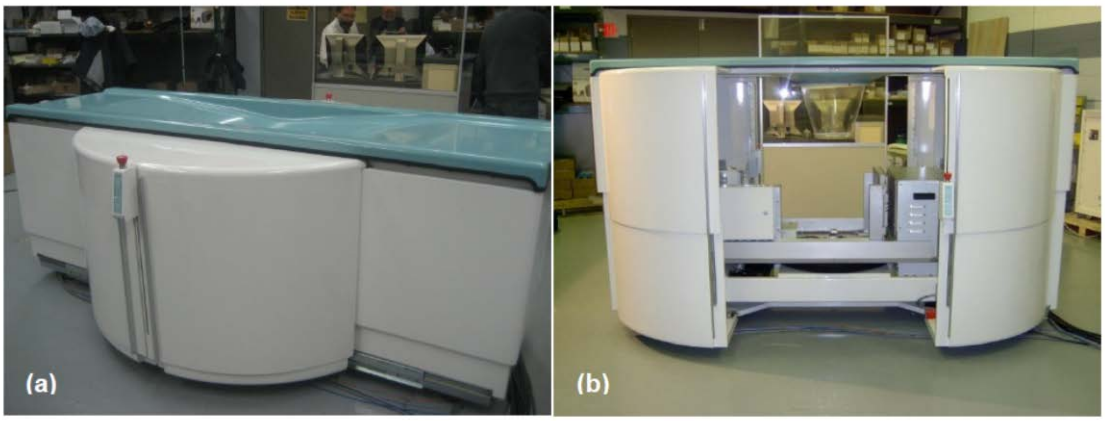


Fig. 1 KBCT system: (a) the system with the gantry door closed; (b) the system with the patient table elevated and both gantry doors open. This allows 1 meter wide access to the gantry interior from both sides for patient procedures (ex. Biopsy) and servicing.

The patient table is mounted above the rotating tube/detector assembly and has an opening to allow one breast to hang pendant in the imaging area at the rotation axis. It has been ergonomically designed to facilitate breast positioning to obtain coverage of the entire breast. The tube/detector assembly rotates around the rotation axis and acquires 300 two-dimensional (2D) projection images in ten seconds. A three-dimensional volume of the breast is reconstructed from this dataset.

During a KBCT imaging examination, the subject lies prone on the table in a left or right anterior oblique position so that the breast of interest suspends and is positioned through the table opening into the area of image acquisition. Once the subject is positioned, scout images are acquired to verify correct centering and positioning of the breast in the imaging volume and to determine technical factors for image acquisition. For a standard scan acquisition of approximately 300 pulsed projection images (at frame rate of 30 frames per second), the kilovoltage (kVp) and time (ms) remain constant at 49 kVp and 8 ms respectively, whereas x-ray tube current (mA) varies per individual breast. The mA value is automatically determined by the system depending on the breast size and density. Exposure time for a single KBCT acquisition is ten seconds. The projection images are reconstructed into 3D KBCT images with isotropic spatial resolution.

Optional accessories to the KBCT include a biopsy bracket to enable KBCT-guided breast biopsies of suspicious lesions, and a collimator which can be used to limit the x-ray beam to an area of interest thereby reducing the dose to the breast.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for breast cancer diagnosis. These include clinical breast examination, film-screen mammography, digital mammography, contrast enhanced spectral mammography, digital breast tomosynthesis, ultrasound and magnetic resonance

imaging. After an abnormality has been identified on diagnostic imaging, 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 his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The KBCT was CE marked on February 28, 2012, received the Canadian Medical Device License on April 11, 2014 and received the Australian Register of Therapeutic Goods Certificate on October 2, 2014. The KBCT 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 the device. These potential adverse effects are common to all x-ray mammography systems:

- Excessive x-ray exposure
- Electrical shock

There were no adverse events that occurred in the clinical studies.

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 may result in delay in diagnosis and progression of disease.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Koning has conducted several types of bench feasibility testing. These include phantom studies for dose estimation and lesion conspicuity. These studies demonstrate pre-clinical feasibility that the KBCT has sufficient contrast and spatial resolution to detect calcifications and masses.

Dosimetry of KBCT vs. DxM. The evaluation of an imaging device that uses ionizing radiation requires careful consideration of the balance between the benefit of the device, usually the quality and clinical utility of the images it produces, and the associated risk, which is normally the radiation insult to the patient required to obtain the images. Thus it is important that the patient dose be estimated by appropriate methods.

Koning has addressed the issue of dosimetry in the KBCT compared to diagnostic mammography (DxM) by following the generally accepted computational approach of using Monte Carlo methods to determine the conversion factors from exposure or air kerma,

measured at a well-defined location relative to the phantom, to average dose to the glandular tissue in the (numerical) phantom. Koning has also used a range of phantoms, and parameterized the results so that conversion factors for breasts of various sizes can be obtained from the model. This method is appropriate and produces reasonably accurate dose values that can be used in considering the risk/benefit tradeoff of the system.

This method was used to estimate patient dose in the KBCT vs DxM in a subset of patients used for the clinical reader study discussed in Section X. Table 1 summarizes the dose analysis, and Figure 2 graphically displays the dose values from their study. Note that the dose estimates for DxM do not include the standard 2 view mammograms (Craniocaudal (CC) and Mediolateral Oblique (MLO) views).

Table 1: Dose analysis summary for KBCT and DxM.

	KBCT	**DxM**	**Difference**
Number of patients	220	220	
Mean dose (mGy)	10.60	9.57	1.03
Standard deviation	3.89	5.16	
Median dose (mGy)	9.85	8.67	1.18
***p* value**			0.01

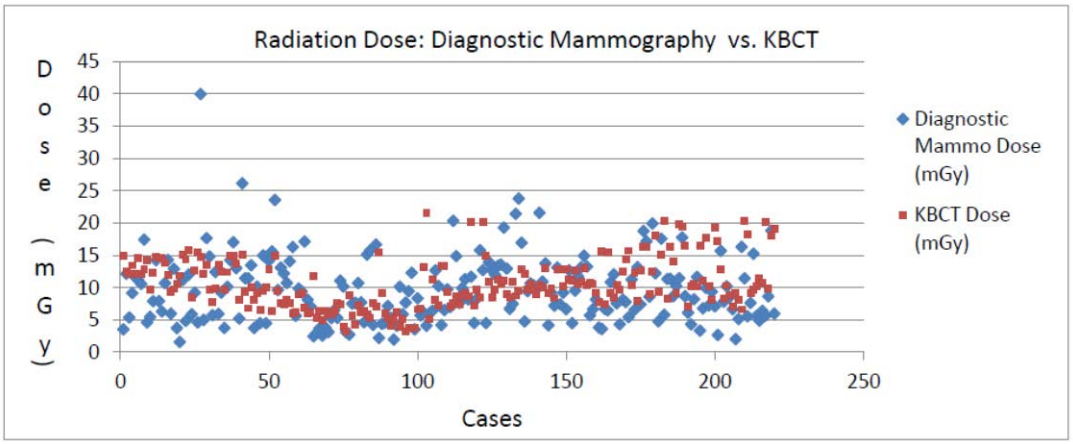


Figure 2. Comparison of KBCT dose to DxM dose for each patient. The KBCT dose is within the range of diagnostic mammography doses.

This data demonstrates that there is a statistically significant increased dose in the KBCT vs. DxM of 1.03 mGy, while the overall dose range is comparable and the dose values are less variable for the KBCT. The potential benefits, including the 3D images in a diagnostic population and less variable dose, were considered to be acceptable against the higher average dose.

***KBCT-guided biopsy*.** The breast biopsy bracket is an optional accessory for the KBCT intended to be used to enable a KBCT guided biopsy procedure using standard KBCT imaging and standard commercial vacuum assisted percutaneous core breast biopsy systems.

The KBCT guided biopsy involves three scans, a pre-biopsy scan to localize the lesion, a confirmatory scan to verify positioning of the needle, and a post-biopsy scan to confirm lesion targeting. Koning has performed a biopsy phantom study with the purpose of evaluating (i) the targeting capacity of KBCT and the biopsy bracket, and (ii) comparing the dose administered with KBCT guided biopsy and stereotactic biopsy. The phantom study included a small, medium and large size biopsy phantom. Each phantom included 30 mass and 15 calcification clusters, respectively. Table 2 summarizes the targeting performance:

Table 2: Phantom-based targeting performance in masses and calcifications in KBCT guided biopsy and stereotactic guided biopsy.

	Stereotactic-guided biopsy	**KBCT-guided biopsy**
Masses: successful retrieval	100% (30/30)	100% (30/30)
Masses: size measurement accuracy within ± 20% of theoretical size range	83% (25/30)	97% (29/30)
Calcification clusters: successful retrieval	100% (15/15)	100% (15/15)
Calcification clusters: size measurement accuracy within ± 20% of theoretical size range	7% (1/15)	73% (11/15)

These results suggest that the KBCT-guided biopsy can improve targeting of masses and calcifications compared to stereotactic-guided biopsy, possibly because of the 3D imaging capability of KBCT. The dose study used estimates of mean glandular dose from each modality after exposure. It assumes that at least 9 images are generally required for each stereotactic-guided biopsy procedure. Based on these methods, Koning reports the following dose estimates:

Table 3: Phantom-based dose estimation for KBCT guided biopsy and stereotactic guided biopsy.

Modality	Dose per image (or scan) Average (mGy)		# of images (or scans)		Average Dose (mGy)	
	Small	Medium	Small	Medium	Small	Medium
Stereotactic	3.8	6.9	9	9	34.2	62.5
KBCT	5.1	10	3	3	15.4	30.0

In summary, KBCT guided biopsy is an appropriate accessory for the KBCT system, as it represents an effective option to workup findings. The biopsy bracket exhibits similar or improved targeting capability as stereotactic guided biopsy at comparable or lower doses, which is a benefit of the KBCT over stereotactic guided biopsy.

B. Additional Studies

Performance standards: The following list of performance standards are met by the KBCT:

Standard	Title
IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007)	Medical Electrical Equipment, Part 1: General Requirements for Safety, 3rd Edition
IEC 60601-1-1:2000	Medical Electrical Equipment – Part 1-1: General Requirements for Safety – Collateral Standard: Safety Requirements for Medical electrical Systems
IEC 60601-1-2:2007	Medical Electrical Equipment – Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests, 3rd Edition
IEC 60601-1-3:2008	Medical Electrical Equipment – Part 1: General Requirements for Safety – 3. Collateral Standard: General Requirements for Radiation Protection in Diagnostic X-Ray Equipment, 3rd Edition
IEC 60601-1-4:2000	Medical Electrical Equipment – Part 1-4: General Requirements for Safety – Collateral Standard: Programmable Electrical Medical Systems
IEC 60601-1-6:2010 IEC 62366:2007	Medical Electrical Equipment – Part 1-6: General Requirements for Safety – Collateral Standard: Usability, including IEC 62366: Application of usability engineering to medical devices, 3rd Edition
EC 60601-2-32:1994	Medical Electrical Equipment Part 2: Particular Requirements for the Safety of Associated Equipment of X-Ray Equipment
IEC 60601-2-44:2009	Medical Electrical Equipment – Part 2-44: Particular Requirements for the Safety of X-ray Equipment for Computed Tomography, 3rd Edition
IEC 60601-2-45:2011	Medical Electrical Equipment – Part 2-45: Particular Requirements for the Safety of Mammographic X-Ray Equipment and Mammographic Stereotactic Devices, 3rd Edition

Software: Koning provided design and software testing documentation consistent with FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. Koning 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. All the test activities were completed successfully.

Tissue coverage, image quality and patient comfort: Koning has also conducted a limited clinical evaluation of tissue coverage, image quality and patient comfort for the KBCT vs. mammography, and has reported their findings in the American Journal of Roentgenology in 2010 [1]. This study demonstrates improved lesion conspicuity, improved breast tissue coverage (better in the inferior, posterior, medial and lateral regions), improved patient comfort (because of lack of compression) and decreased sensitivity of calcification type lesions. This study highlights potential benefits of the KBCT vs. DxM of improved tissue coverage and patient comfort, and a potential limitation in the setting of calcifications.

Conclusion of Non-Clinical Testing

The bench and non-clinical testing demonstrates that the KBCT can produce diagnostic quality breast CT images at a dose comparable to DxM. This testing also demonstrates

some potential benefits of the KBCT compared to DxM including a less variable dose range, improved patient comfort, improved tissue coverage and improved biopsy targeting capacity at lower dose.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of KBCT for diagnostic breast imaging for breast cancer in the US. Data from this clinical study along with an assessment of the clinical benefits of the device 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	Prospective subject accrual	Subject accrual for blinded reader study Evaluate the safety of the device	2 enrollment sites, 3 IRB protocols	478 patients
Blinded Image Evaluation, Multi-Reader Multi-Case (MRMC) study	Blinded reader study; partially randomized controlled clinical trial on an enriched case set	Evaluate the safety and effectiveness of the device Primary endpoint: Evaluate the diagnostic performance of the KBCT and DxM as measured by areas under the receiver operating characteristic (ROC) curve (AUC)	18 readers	235 cases (156 noncancers, 79 cancers)

A. Case Acquisition Study

Koning designed and conducted a prospective clinical case acquisition study to collect diagnostic mammography (DxM), 2 view mammography (2VM) (CC and MLO views) and KBCT images to be used for the pivotal reader study. Note that the patients enrolled in these studies were from a diagnostic population—i.e., women who had abnormal previous imaging findings, or had signs or symptoms of breast cancer. In general, diagnostic imaging workup yields a final BIRADS determination of 1-5, with BIRADS 4 and 5 patients proceeding to biopsy and BIRADS 3 patients proceeding to short term follow-up.

A total of 478 patients were enrolled from 3 United States clinical sites under 3 IRB approved clinical case acquisition protocols:

- RSRB #0000141117: Subjects enrolled under this protocol were classified as BIRADS 3 after diagnostic workup, or had findings suspicious for malignancy (e.g., BIRADS 4 or 5 after diagnostic workup, have a palpable abnormality, a suspicious finding on imaging, or are scheduled for biopsy)
- RSRB#00029991: Subjects enrolled under this protocol were scheduled for biopsy of suspicious findings after being classified as BIRADS 4 or 5 after diagnostic workup
- WIRB #20071915: Subjects enrolled under this protocol had findings suspicious for malignancy (e.g., BIRADS 4 or 5 after diagnostic workup, have a palpable abnormality, a suspicious finding on imaging, or are scheduled for biopsy)

The accrual patient population was enriched with BIRADS 4 and 5 cases.

The accrual sites for the cases collected were:
- Elizabeth Wende Breast Care (EWBC), Rochester, NY (WIRB #20071915)
- University of Rochester Medical Center (URMC), Rochester, NY (RSRB #000014117, RSRB #00029991)

All enrolled subjects had standard two-view mammograms (2VM) (CC and MLO views) and diagnostic views before or upon enrollment. Enrolled subjects obtained KBCT examination.

1. Clinical Inclusion and Exclusion Criteria

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

	RSRB # 0000141117	RSRB # 00029991	WIRB #20071915
BI-RADS® 1, 2 Cases	None (no diagnostic cases enrolled)	None (no cases enrolled)	Before 12/13/2010: • No diagnostic cases enrolled for BIRADS 1, 2, 3 • Same inclusion criteria for BIRADS 4, 5 cases as for other two protocols After 12/13/2010: • at least 35 years of age of any ethnicity • Require diagnostic imaging • Will undergo study imaging within four weeks from date of diagnostic mammogram, and prior to breast biopsy if a biopsy is scheduled • Is able to provide informed consent
BI-RADS ® 3 Cases	• Are at least 40 years of age of any ethnicity • Had a routine mammogram, read as BI-RADS® 3	None (no cases enrolled)	
BI-RADS® 4, 5 Cases	• At least 40 years of age of any ethnicity • Have a palpable abnormality detected by Breast Self Exam (BSE), or Clinical Breast Exam (CBE) or have a non-palpable abnormality detected by an imaging modality • After diagnostic work-up are categorized as BI-RADS® 4 or 5. • Are scheduled for biopsy either by large gauge needle biopsy or excisional biopsy. • Will undergo study imaging prior to biopsy and within four weeks of diagnostic work-up	• Age 40 or older, • Scheduled for biopsy after classification as BI-RADS 4 or 5 and have had a screening or diagnostic full-field digital mammography exam • • Able to provide informed consent	

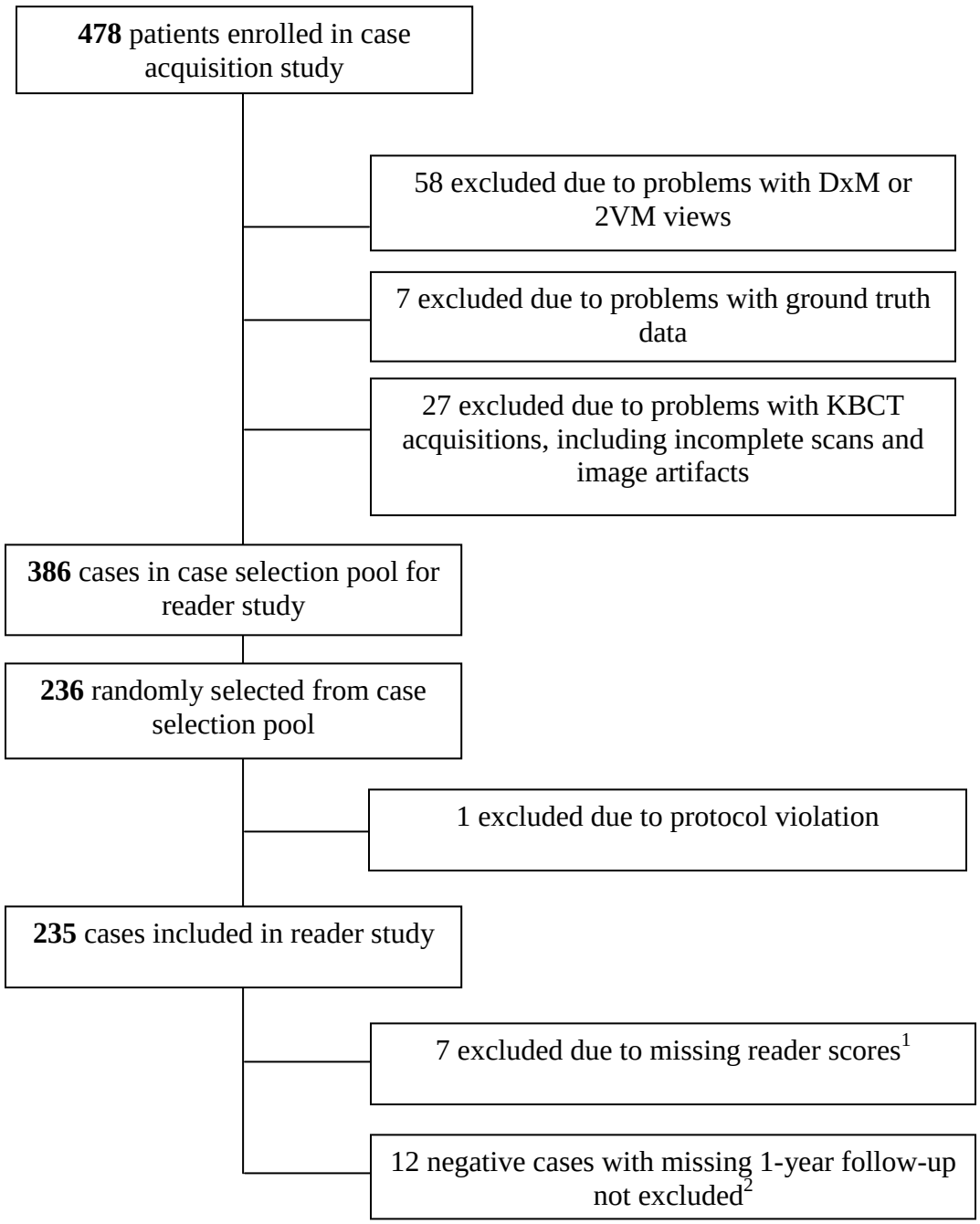
Patients were <u>not</u> permitted to enroll in the KBCT study if they met any of the following exclusion criteria:

- Pregnancy
- Lactation
- Subjects with physical limitations that may prohibit resting prone on the exam table, such as, but not limited to: frozen shoulder, recent heart surgery, pace maker
- Subjects who are unable to tolerate study constraints
- Subjects who have received radiation treatments to the thorax for malignant and nonmalignant conditions, such as (but not limited to)
    - Treatment for enlarged thymus gland as an infant
    - Irradiation for benign breast conditions, including breast inflammation after giving birth
    - Treatment for Hodgkins disease
- Subjects who have participated in a prior breast clinical trial that gave additional radiation dose, such as an additional mammogram
- Subjects who have received large numbers of diagnostic x-ray examinations for monitoring of disease such as (but not limited to)
    - Tuberculosis

- Severe scoliosis

2. Follow-up Schedule
   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



1 Koning performed an analysis by imputing POM scores for these missing cases, which yielded results consistent with the primary analysis.
2 Koning performed an analysis by imputing a positive truth for the patients with incomplete follow-up which yielded results consistent with the primary analysis

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a diagnostic breast imaging study performed in the US, and are representative of a diagnostic population. The following tables summarize some pertinent patient demographics and characteristics for the 235 cases included in the reader study analysis:

Table 4: Age distribution for cases in the reader study.

	EWBC	URMC
Number of subjects	134	101
Age range (years)	36-82	40-84
Average age (years)	54.57	54.01
Standard deviation (years)	10.08	9.79

Table 5: Breast density distribution for cases in the reader study.

	EWBC	URMC	Total
Almost entirely fat	3	6	9 (3.8%)
Scattered fibroglandular tissue	53	37	90 (38.3%)
Heterogeneously dense	74	42	116 (49.4%)
Extremely dense	4	16	20 (8.5%)
Total	134	101	235 (100%)

The 235 cases included in the MRMC analysis study represent 262 screening recall cases (i.e., patients with BIRADS 0 at screening) and 123 patients presenting with a complaint or referral. It consists of a higher proportion of BIRADS 4 and 5 cases (77%) than BIRADS 1,2 or 3 cases (23%), and 79 cancers and 156 non-cancers:

Table 6: Summary of cancers and non-cancers for cases in the reader study

	Negative	Benign	Cancer	Total
Number	52	104	79	235

These attributes are consistent with an enriched diagnostic patient population. Note that during the acquisition phase of the study a total of 4 cancers were detected on KBCT that were not seen on DxM.

D. Reader Study Design and Methods

The sponsor performed a retrospective multi-reader multi-case (MRMC) study to evaluate the reader performance of KBCT + standard two view mammograms (2VM) (CC and MLO views) and DxM in a diagnostic population. The MRMC study consisted of 18 readers (varying experiences) and 235 cases (156 benign or negative, 79 malignant)

derived from a diagnostic population (BIRADS 1-5 after diagnostic workup including DxM).

The primary objective was to calculate the area under the ROC curve of KBCT+2VM and DxM as a measure of reader performance. The probability of malignancy (POM) score (ranging from 0-100%) was used for the primary analysis. This was a case-based measure, wherein an overall POM score was assigned to the entire case (rather than to each lesion).

Secondary objectives included comparing KBCT alone vs. KBCT+2VM, sensitivity and specificity analysis, lesion based free-response ROC (FROC) analysis and subgroup analysis (lesion type, breast density, lesion size, study center).

1. Reference Standards

The establishment of ground truth was based on a combination of 1-year follow up and biopsy results.

- For negative subjects, ground truth was established on one year follow-up results.
- For benign subjects, ground truth was established based on biopsy/histology results or one-year follow-up.
- For cancer subjects, ground truth was established on the biopsy/histology results.

The following criteria were used to assess true negative (TN), true positive (TP), false positive (FP) and false negative (FN) findings:

- Negative cases and benign cases for which a reader identified no significant lesions were counted as true negatives (TN)
- Negative cases and benign cases for which a reader identified one or more lesions were counted as false positives (FP)
- Cancer cases for which a reader identified no lesions were counted as false negatives (FN)
- Cancer cases for which a reader identified one or more lesions were classified as:
  TP with correct location with respect to biopsy-proven malignancies for the location-based ROC analysis

2. Readers

The MRMC study consisted of a total of 18 MQSA-certified readers representing a range of clinical experience. Training consisted of a 1-day training session in the operation of the KBCT workstation and the correct interpretation of KBCT images. An introduction to KBCT was provided, including a series of 15 training cases, in a 1:1 ratio of cancer to benign. At the end of the training session, readers scored 15 independent cases, in a 1:1 ratio of cancer vs. normal or negative cases. No readers were excluded from the study.

3. Image Scoring

Readers were blinded to the details of the patient histories. A cross-over design with a wash-out period of at least four weeks was employed. Cases were randomized into two groups that were read in a different modality in each of the two reading sessions

(Table 8), and within each reading session the order in which the cases were read was randomized.

Table 7: Cross-over study design—modality reading for each reading session and each group

Reading Session	**Group**	
	A	**B**
1	i) KBCT ii) KBCT +2VM	DxM
2	DxM	i) KBCT ii) KBCT + 2VM

For each case the following readings were made:

- DxM: This reading includes the 2VM reading as well as the additional mammographic views taken for diagnosis
- KBCT: The first reading of KBCT data was performed without the 2VM
- KBCT+2VM: This was followed immediately by reading the KBCT with the 2VM

For each of the image sets, the reader examined the images and looked for areas of concern, i.e., the reader was not provided the lesion location. The reader was asked to mark the lesion and assign BI-RADS ratings (1-5) and a probability of malignancy (POM) score ranging from 0-100. After marking and rating all lesions, the reader was asked to assign an overall BI-RADS rating and POM score for the whole case. This overall rating was used in the primary analysis for case-based ROC analysis. Note that this study used a forced BIRADS determination (i.e., BIRADS 0 is not permitted).

4. Receiver Operating Characteristics (ROC) Analysis

A multi-reader, multi-case (MRMC) ROC analysis using the POM 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) MRMC method. Case-based ROC analysis was employed in the primary analysis, while lesion-based FROC analysis was employed in a secondary analysis.

E. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the 478 patients/procedures in the case acquisition study. There were no reportable adverse events.

2. Effectiveness Results: Primary Analysis

   The primary analysis was evaluating the reader performance case-based AUC for KBCT + 2VM and DxM for 18 readers and 235 cases. The study results demonstrated the following, which was also confirmed by FDA analyses:

Table 8: Summary of primary analysis.

		AUC Estimate	Standard Error	95% Confidence Interval
Empirical Estimations	**DxM**	0.792	0.027	[0.739,0.844]
	KBCT+2VM	0.791	0.026	[0.740,0.841]
Parametric Estimation	**DxM**	0.796	0.025	[0.746,0.844]
	KBCT+2VM	0.796	0.025	[0.747,0.845]

The AUC difference (KBCT+2VM)-DxM was -0.001 with standard error 0.017 for empirical estimation, and 0.001[1] with standard error 0.015 for parametric estimation. The following plot graphically displays the overall ROC curves for KBCT+2VM and DxM.

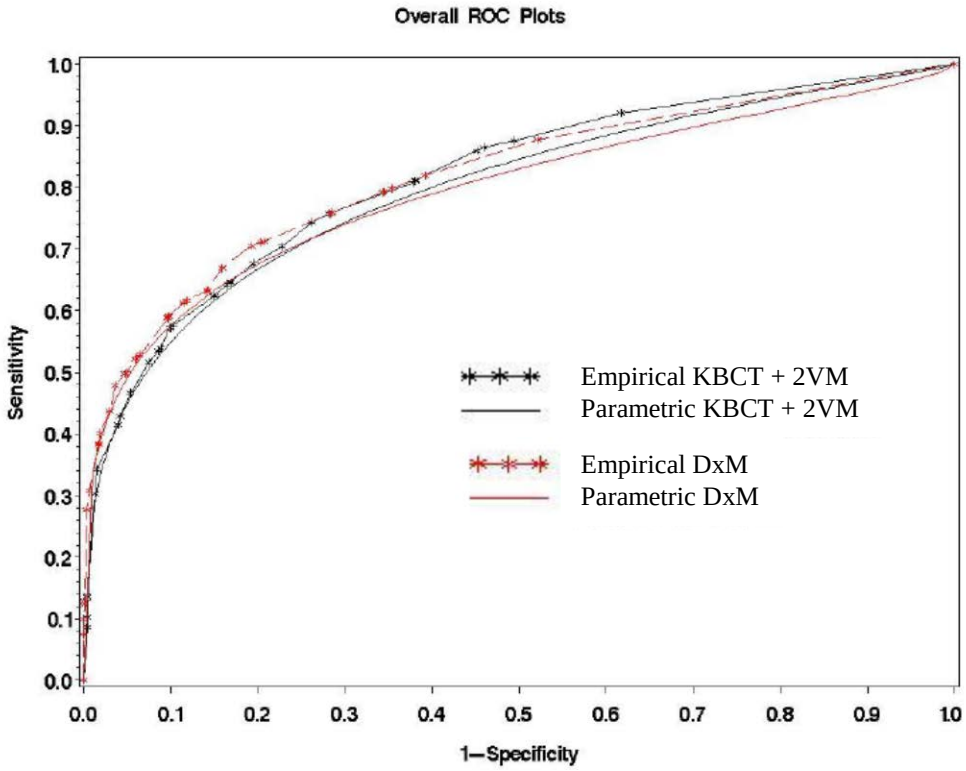


Figure 3. Overall ROC curves for all 18 readers.

[1] Due to rounding error, this value is not the same as the difference based on the displayed AUC values in the Table.

The AUC estimate 0.791 for KBCT+2VM and the difference in AUC -0.001 from DxM with standard error 0.017 are clinically acceptable for a diagnostic imaging modality in a diagnostic patient population. The empirical ROC curves for KBCT+2VM and DxM cross and overlap for false positive fractions (FPFs) 0.3-0.4, approximately, with KBCT+2VM tending to perform worse below this interval and better above this interval. However, according to bootstrap analysis, the partial AUC for $0 < FPF < 0.3$ was not significantly worse for KBCT+2VM than DxM.

3. Effectiveness Results: Secondary and Subgroup Analyses

KBCT vs. KBCT+2VM: As noted above, readers performed a reading of KBCT alone, without 2VM. The purpose of this reading was to detect any difference in the AUC if KBCT images are read with vs. without the 2VM.

Table 9: Summary of analysis for KBCT read alone and with 2VM.

		AUC Estimate	**Standard Error**	**95% Confidence Interval**
Empirical Estimations	**KBCT alone**	0.770	0.026	[0.718, 0.821]
	KBCT+2VM	0.791	0.026	[0.740,0.841]
Parametric Estimation	**KBCT alone**	0.779	0.025	[0.730,0.828]
	KBCT+2VM	0.796	0.025	[0.747,0.845]

The AUC difference (KBCT alone)-(KBCT+2VM) was -0.021 with standard error 0.017 for empirical estimation, and -0.017 with standard error 0.015 for parametric estimation. A decrease in AUC was observed for KBCT reading without 2VM compared to with 2VM. These results underscore the statement in the Indications for Use that KBCT images should be read along with 2VM (CC and MLO views).

Sensitivity/Specificity: Another secondary objective was to determine whether there is any difference in sensitivity and specificity between the KBCT+2VM and DxM. Sensitivity is defined as the percentage of cancer cases whose diagnostic exam (KBCT+2VM or DxM) was positive, using either greater than or equal to BIRADS 3 or BIRADS 4 rating as a cut-point. Specificity is defined as the percentage of non-cancer cases whose diagnostic exam was either negative or benign using less than BIRADS 3 or BIRADS 4 as a cutpoint. This information is summarized in Table 10.

Table 10: Summary of secondary sensitivity/specificity analysis (shown are average % and [95% CI], and difference in %).

	KBCT+2VM	DxM	Difference
BIRADS ≥4 sensitivity	88.03 [85.54, 90.15]	82.78 [79.74, 85.44]	5.25
BIRADS <4 specificity	34.45 [31.76, 37.25]	41.00 [38.12, 43.94]	-6.55
BIRADS ≥3 sensitivity	92.44 [90.37, 94.10]	88.74 [86.13, 90.92]	3.70
BIRADS <3 specificity	30.31 [26.49, 34.42]	31.39 [27.49, 35. 57]	-1.08

These results suggest an improvement in sensitivity for KBCT+2VM compared to DxM using either BIRADS 3 or 4 as a cut point, and a decreased specificity for KBCT+2VM compared to DxM when using BIRADS 4 as a cut point.

Lesion based FROC analysis: The lesion-based FROC analysis is summarized in Table 11:

Table 11: Summary of secondary lesion-based FROC analysis.

	FROC Figure of Merit	Standard Error
(KBCT+2VM)-DxM	-0.068	0.0187

This analysis appears to be inconsistent with the case-based ROC analysis performed for the primary analysis. This discordance appears to be due to the higher number of false positives identified by the KBCT. This highlights a potential risk of the KBCT compared to DxM.

An increase in false positives raises the concern that more KBCT patients will be subject to the risk of unnecessary biopsies of benign lesions compared to those who obtain DxM. Additional investigation regarding how the lesion specific ratings (used for the secondary FROC analysis) compared to the over-all patient ratings (used in the primary ROC analysis) given by the readers in the MRMC study was performed. In almost every reading by every reader the overall rating given to the patient was equal to the maximum rating given to one of the lesions in the patient image. In less than 1% of the 4247 readings were the lesion-specific ratings higher than the overall ratings given to the images. Therefore the additional false positive marks that cause the difference between the FROC and ROC analyses have POM ratings that are less than those used in the case-based primary ROC analysis. Because these ratings are lower, they are unlikely to change the decisions to send patients to biopsy. Therefore, although the FROC results presented by the sponsor suggests that more lesions may be unnecessarily biopsied, they

do not indicate that the use of the KBCT would lead to higher biopsy rates of women, thereby mitigating the primary potential risk suggested by the FROC analysis.

Analysis by lesion subtype (calcification or mass): There were 93 calcification cases (18 malignant, 75 benign/negative) in the MRMC study. The study was not powered to do a formal statistical evaluation of performance within the setting of calcifications. However, the study data suggests that KBCT has overall reduced diagnostic accuracy in calcification type lesions:

Table 12: Summary of secondary analysis of AUC by lesion subtype.

Lesion Type	KBCT +2VM	DxM	Difference (KBCT+2VM)-DxM	Standard Error
Calcification	0.713	0.757	-0.043[2]	0.031
Mass	0.831	0.833	-0.001[2]	0.017

This reduced performance highlights a potential limitation of the KBCT. Note that the performance of KBCT read alone in the setting of calcifications was even further reduced, underscoring the statement in the Indications for Use that these images should be read along with 2VM.

Analysis by lesion size: Sensitivity analysis by lesion size was performed, using greater than or equal to BIRADS 4 as a cut-point. The study was not powered to evaluate statistical differences in sensitivity by lesion size. The following table summarizes these results:

Table 13: Summary of secondary lesion size analysis.

Reading	Sensitivity in lesions ≤ 12mm	Sensitivity in lesions > 12 mm
KBCT + 2VM	91.1%	87.0%
DxM	84.4%	86.0%

There was improvement in KBCT+2VM vs. DxM sensitivity for smaller lesions ≤ 12mm (91% vs. 84%). This highlights a potential benefit of the KBCT system.

Analysis by breast density: The diagnostic performance with respect to breast density is summarized below, suggesting a trend for improved performance in less dense breasts as shown in Table 14. The study was not powered to evaluate statistical differences in sensitivity by breast density.

[2] Due to rounding error, this value is not the same as the difference based on the displayed AUC values in the Table.

Table 14: Summary of secondary breast density analysis.

Breast density	KBCT +2VM	DxM	Difference (KBCT+2VM)-DxM	Standard Error
Almost entirely fat or scattered fibroglandular tissue	0.846	0.828	0.018	0.023
Heterogeneously or Extremely Dense	0.736	0.757	-0.021	0.023

Additional analyses: There were 7 cases excluded from the 235 MRMC reader study cases due to missing reader scores. Koning performed an analysis by imputing POM scores for these missing cases, which yielded results consistent with the primary analysis. In addition, there were 12 negative cases with missing 1-year follow-up that were not excluded from the analysis. Koning performed an analysis by imputing a positive truth for these patients with incomplete follow-up which yielded results consistent with the primary analysis

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 18 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 average reader performance of KBCT + 2VM and DxM is as shown in Table 8, with an empirical estimate of AUC as 0.791 and 0.792, respectively, and a difference of -0.001.

The AUC estimate for KBCT+2VM and the difference in AUC from DxM are clinically acceptable for a diagnostic imaging modality in a diagnostic patient population. Therefore, the primary clinical study demonstrates that the KBCT+2VM has reasonable effectiveness in a diagnostic population.

B. Safety Conclusions

The risks of the device are assessed 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 no adverse events 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 diagnostic mammography.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on bench data and data collected in a clinical study conducted to support PMA approval as described above. Overlapping tissue presents a problem in conventional two-dimensional mammography. The role of a 3D x-ray breast imaging technique such as breast CT is to improve the visibility of regions of the breast where a cancer could be obscured by overlapping tissue. In addition, the preclinical studies demonstrate that KBCT may offer improved tissue coverage compared to mammography, allowing the radiologist to evaluate more breast tissue. Observations based on the secondary analyses of the reader study suggest an improvement in sensitivity, including for small lesions ≤12mm. Additionally, during the case acquisition portion of the study, it was observed that the KBCT was able to detect a small number of cancers that were not found on mammography. In a diagnostic population, such improvements could lead to the earlier diagnosis of cancer. A caveat is that the study was not powered to draw conclusions based on these observations, but they do highlight potential benefits of the device.

Beyond potential improvements in the identification of cancerous lesions, the KBCT system has other possible l patient benefits. For example, the preclinical studies demonstrate that patients could benefit from the enhanced comfort experience of the KBCT compared to mammography because KBCT acquisitions do not require breast compression. In addition, the bench testing data provided by the sponsor suggests that the KBCT-guided breast biopsy system can improve the targeting of suspicious breast lesions, with comparable or lower dose compared to stereotactic-guided biopsy. Finally, although the average dose was higher with the KBCT than diagnostic mammography, the typical dose range was less variable. This is likely due to the fact that in some patients it may take many diagnostic mammography acquisitions to adequately work up the finding of interest, and it is in general not

possible to identify such patients ahead of time. Therefore, the KBCT offers the benefit that physicians and patients will have a better idea of the expected dose prior to the examination.

Additional factors to be considered in determining probable risks and benefits for the KBCT device included the consideration that 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 proposed device. The lesion-based FROC analysis suggests an increased false positive fraction compared to DxM, although the data does not suggest more patients will be unnecessarily biopsied (although more lesions may be). However, note that it may be difficult to translate the estimates of sensitivity and specificity from the MRMC study into clinical practice because of the enriched study population.

In general, the risk of a false positive is similar to that of other breast imaging devices intended for diagnosis. In clinical practice, a false positive could lead to an unnecessary biopsy of a benign lesion. However, there are a few factors that can reduce our concern regarding this risk. Firstly, in a diagnostic population additional imaging tools (e.g., ultrasound) would be available to help refine false positive and negative assessments in a way that could not be captured in this MRMC study where a forced BIRADS determination was utilized. Secondly, it could be that with increased familiarity with the KBCT, the proportion of false positives could decrease. Finally, it is important to note that performing biopsies of benign lesions is an already accepted risk of diagnostic workup of patients in a diagnostic population, whose lesions will be biopsied if the probability of malignancy is greater than 2% (i.e., BIRADS 4 or higher).

Another risk is the dose delivered to the patient. The dose range of KBCT appears to be comparable to DxM, although the average dose is higher by 1.03 mGy. This does not pose a significant concern, because in current practice, dose limitations are not imposed on the workup and resolution of a patient presenting for diagnostic imaging. Furthermore, as noted above, the expected dose range is less variable with the KBCT compared to diagnostic mammography, which is a potential advantage.

In conclusion, given the available information above, the data support that for diagnostic breast imaging the probable benefits outweigh the probable risks.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on January 14, 2015. The final conditions of approval cited in the approval order.

The applicant's manufacturing facilities have 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

[1] Connell A, Conover D, Zhang Y, et al., Cone-Beam CT for Breast Imaging: Radiation Dose, Breast Coverage, and Image Quality, AJR 2010; 195:1–14, August 2010.