SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Optoacoustic Breast Imaging System

Device Trade Name: Imagio® Breast Imaging System

Device Procode: QNK

Applicant's Name and Address: Seno Medical Instruments, Inc.
8023 Vantage Drive, Suite 1000
San Antonio, TX 78230

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200003

Date of FDA Notice of Approval: 01/11/2021

II. INDICATIONS FOR USE

The Imagio Breast Imaging System is indicated for use by a trained and qualified healthcare provider for evaluation of palpable and non-palpable breast abnormalities in adult patients who are referred for a diagnostic imaging breast work-up, following clinical presentation or either screening or diagnostic mammography or other imaging examinations. The ultrasound mode should be initially used in a targeted fashion, to assess any focal area(s) of clinical or imaging concerns. In ultrasound mode, the device can be used to assign a BI-RADS category to either breast tissue or a mass that is causing clinical or imaging concerns. Masses that are classified as BI-RADS categories 3 through 5 can then be assessed using the Opto-Acoustic (OA) mode. In the OA mode, the Imagio Breast Imaging System provides information about the central nidus, boundary and peripheral zones, based on vascularity and blood oxygen saturation of the imaged tissues, to assist in the diagnosis of the benign or malignant mass(es) of interest. For ultrasound BI-RADS 3-5 masses, using the OA features of the mass allows for improved classification of the mass of interest as compared to ultrasound alone. The OA mode is not indicated for ultrasound BI- RADS 1 and 2 findings. The Imagio Breast Imaging System includes an artificial intelligence (AI) based software function to assist the users in assessing the BI-RADS Classifications.

This device is not intended to be used as a replacement for mammographic screening or for definitive pathologic diagnosis.

III. CONTRAINDICATIONS

Absolute contraindications are as follows:

- Is pregnant.
- Has open sores including insect bites, rash, poison ivy, and chafing on the skin of the ipsilateral breast.
- Is experiencing phototoxicity associated with currently taking, or having taken, photosensitizing agents within the previous 72 hours such as sulfonamides, ampicillin, tetracycline.
- Is currently undergoing phototherapy.
- Has a history of any photosensitive disease (e.g., porphyria, lupus erythematosus) or is undergoing treatment for a photosensitive disease and is experiencing photosensitivity.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Imagio Breast Imaging System labeling.

V. DEVICE DESCRIPTION

The Imagio Breast Imaging System (Figure 1) is a diagnostic functional and morphologic imaging system that combines optoacoustic (OA) imaging with conventional diagnostic ultrasound (US) imaging to aid in diagnostic evaluation of breast lesions. The Imagio Breast Imaging System acquires, processes, and displays co-registered OA and US images to provide structural and functional information about breast abnormalities in real-time. OA/US imaging technology combines the high contrast resolution of optical imaging with the high spatial resolution and deep penetration of ultrasound imaging.

Figure 1: Imagio Breast Imaging System

In OA imaging (also known as photoacoustic imaging in the literature), short nanosecond pulses of laser light are delivered into tissue. When that light is absorbed, for instance by hemoglobin molecules found in blood, those molecules undergo thermoelastic expansion and generate acoustic pressure signals that can be detected at the tissue surface using a hand-held probe (Figure 2). The probe has optical windows that deliver light to tissue and an array

of piezoelectric transducers that detect acoustic signals. The received OA signal increases with both the absorption strength and concentration of light-absorbing molecules. Two strong absorbers in tissue are oxygenated and deoxygenated hemoglobin found in blood vessels. By performing OA imaging using two near-infrared optical wavelengths (757 nm and 1064 nm) for which oxygenated and deoxygenated hemoglobin absorb light differently, the Imagio Breast Imaging System can estimate the relative oxygen saturation of hemoglobin in tissue.

Figure 2: Optoacoustic (OA/US) Probe and Probe Head

In addition to OA imaging, the Imagio Breast Imaging System provides conventional ultrasound imaging capabilities such as 2D B-mode (amplitude), color Doppler, power Doppler, and pulsed wave Doppler for blood/fluid flow analysis, user-adjustable image display settings, and the ability to measure and annotate images. The Imagio Breast Imaging System can provide overlaid OA/US images that co-register anatomical US B-mode images with functional OA mapped information in real-time. These images are presented as a 6-on-1 (six-up) display (Figure 3). The grayscale US image provides morphologic information, whereas the OA/US images provide both morphologic and functional information. The morphologic information provided by OA/US includes: the presence or absence of detectable blood vessels as well as the number, size, shape, orientation, and polymorphism of blood vessels. The functional information provided by OA/US includes the relative amount of hemoglobin and relative oxygen saturation of hemoglobin.

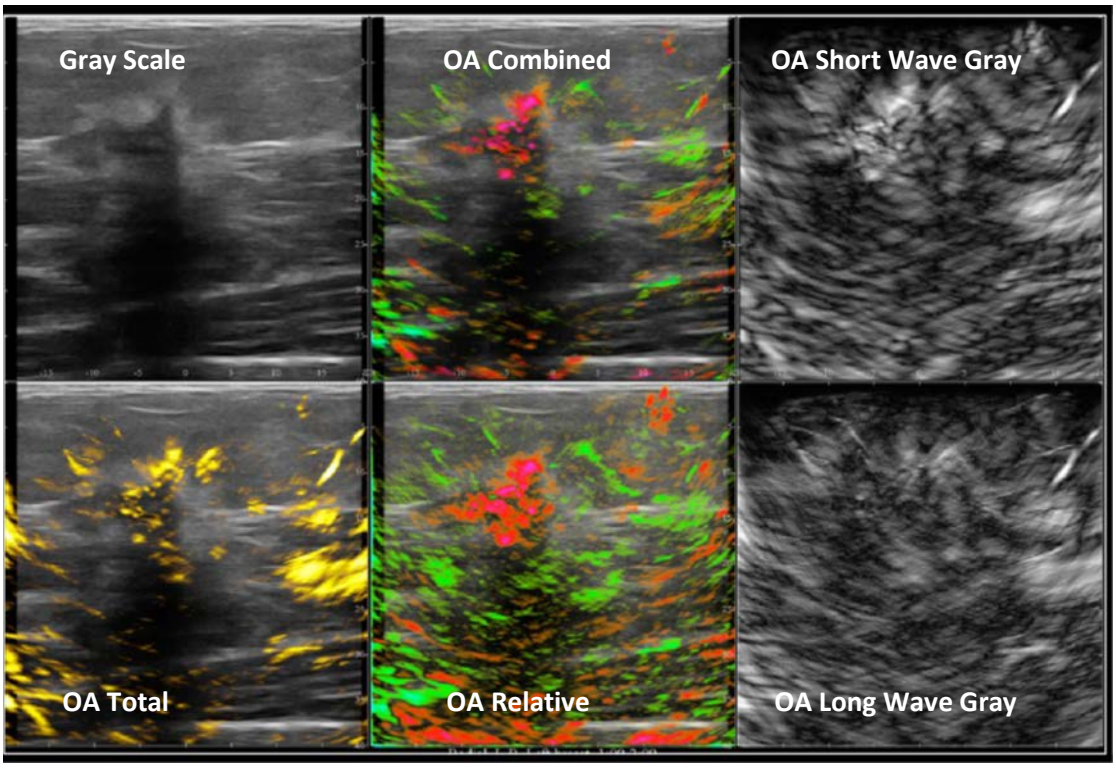

Figure 3: Representative standard 6 on 1 display showing US image (upper left) and various OA mode images. The red/green colorized images (OA Combined and OA Relative) provide oximetry information.

The Imagio Breast Imaging System was determined to be a Class 3B laser product for externally accessible emission from the handheld probe and a Class 4 laser product for internally accessible emission (during device maintenance/service). The Imagio's laser subsystem is comprised of a laser head, laser controller, temperature controller, and foot switch. The laser head generates the pulsed laser emissions, directing them into an optical port which is coupled with a fiber optic cable connecting to the handheld probe. The laser controller provides real time control of laser emission timing and energy levels. The temperature controller regulates the laser head temperature to maintain optimal laser head operation by heating or cooling water that is then pumped through portions of the laser head at a constant flow rate. The foot switch must be engaged by the operator to allow laser light emission. Light is delivered from the fiberoptic cable through two optical windows in the face of the handheld probe to illuminate underlying tissue. During laser light emission, users, patients and observers are required to wear provided laser safety eyewear meeting appropriate optical density specifications.

The ultrasound imaging component of the device is based on conventional, currently-existing ultrasound imaging principles. In fact, ultrasound imaging is achieved using a FDA cleared device, Imagio ultrasound imaging system (K182628). This system supports one probe, L14-5/38, manufactured by Analogic Corporation (previously Ultrasonix) cleared under K089035.

To assist the users in assessing BI-RADS classification, the Imagio Breast Imaging System is used in parallel with a SenoGram™. The SenoGram is a software tool, using machine learning, that helps the radiologist predict the probability of malignancy (POM) based on a set of reader-assigned feature scores and other relevant data. The purpose of the SenoGram is to help the users more accurately combine their various feature scores into a single overall score (POM). Unlike some of the more commonly-used computer-aided diagnosis systems that use medical images as the input, SenoGram input comes from the users. The user enters 5 feature scores for internal ultrasound (IUS), 5 feature scores for OA and 4 other features: subject age, maximum diameter depth to posterior wall of mass, size of lesion, and mammographic BI-RADS density category (where available). IUS above refers to the internal ultrasound functionality of the Imagio Breast Imaging System (i.e., without OA). When all data has been entered, the user interface graphically displays the SenoGram Likelihood/Probability of malignancy (LOM/POM) on a scale of 0 to 100. If the user assigns correct feature scores, then the SenoGram will perform well; if the user assigns incorrect feature scores, then the SenoGram will not perform well. The SenoGram classification model was trained using feature scores from the PIONEER Pivotal Readers (please see below), including feature scores from the expert reader assigned during the PIONEER Pivotal Study.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for breast cancer diagnosis. These include clinical breast examination, mammography, color and power Doppler, strain and shear wave elastography, magnetic resonance imaging, and molecular breast imaging. 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 CE Mark for the Imagio Breast Imaging System was obtained March 30, 2014. Prior to PMA approval, Seno did not commercialize the Imagio Breast Imaging System in any countries. The Imagio Breast Imaging System has not been withdrawn from the market for any reason related to safety or effectiveness.

The ultrasound imaging component of the subject device was cleared under K182628. The probe in this system was by UltraSonix system (SONIX MDP ultrasound scanner) and cleared via K089035.

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.

Potential adverse effects from use of the Imagio Breast Imaging system are common to marketed conventional diagnostic ultrasound imaging devices and topically applied lasers, e.g.:

1. Electrical shock,
2. Laser eye injury,
3. Skin irritation or abrasion,
4. Localized discomfort, tenderness, or tingling,
5. Contact dermatitis,
6. Photosensitivity,
7. Hematoma, and
8. Infection

Both false positive and false negative evaluations, which could result in false diagnosis or misclassification are potential adverse effects. The consequence of a false positive may result in additional imaging or workup that would otherwise not be performed. These additional procedures would carry the same risk of modality exposure, infection, or hematoma as would happen with any false positive evaluation. A false negative could potentially result in a missed or delayed cancer diagnosis and thus delayed treatment.

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

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical laboratory studies were completed on Imagio Breast Imaging System and included system verification and validation testing prescribed by Seno Medical's quality system Design Controls which is compliant with 21 CFR 820.30. This testing ensured that the Imagio Breast Imaging System design met required specifications for safety and effectiveness. No animal studies were conducted. Table 1 presents the nonclinical design verification and validation testing conducted on the Imagio Breast Imaging System.

Table 1. Nonclinical Laboratory Testing

Test	Purpose	Acceptance Criteria	Results
1. Biocompatibility, Cytotoxicity, ISO 10993-5	Biocompatibility of OA/US Probe	Non-cytotoxic Complies with ANSI/AAMI ISO 10993-5. Biological evaluation of medical devices-Part 5: Tests for In vitro cytotoxicity.	Pass
2. Biocompatibility, Skin Irritation, ISO 10993-10	Biocompatibility of OA/US Probe	Non-irritant Complies with ANSI/AAMI ISO 10993-10. Biological evaluation of medical devices-Part 10: Tests for Irritation and skin sensitization.	Pass
3. Biocompatibility, Maximization Sensitization, ISO 10993-10	Biocompatibility of OA/US Probe	Non-sensitizer Complies with ANSI/AAMI ISO 10993-	Pass

		10. Biological evaluation of medical devices-Part 10: Tests for Irritation and skin sensitization.	
4. Reprocessing (cleaning and disinfection procedure) per FDA guidance document: Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling issued on March 2015	Reprocessing of OA/US Probe and entire system	The reprocessing procedures are validated according to the guidance document.	Pass
5. Ultrasonic safety and essential performance testing	Reliability/Functionality and ultrasound safety of OA/US Probe	Complies with IEC60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment.	Pass
6. Probe Reliability/Functionality/Medical electrical equipment safety Testing	Electrical safety of Entire system	Complies with ANSI/AAMI ES60601-1:2005/A1:2012 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	Pass
7. Electromagnetic compatibility (EMC) Testing	EMC testing of Entire system	Complies with IEC 60601-1-2 Edition 4.0 2014-02 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	Pass
8. Laser safety, per IEC 60825-1:2014	Laser safety of subsystem and OA/US probe	Complies with IEC 60825-1:2014, “Safety of laser products –Part 1: Equipment classification and requirements”	Pass
9. Laser Safety Analysis, per ANSI Z136.1:2014	Laser subsystem, OA/US probe, and laser safety eyewear	Measured laser emission (radiant exposure) out of the handheld probe is below Maximum Permissible Exposures (MPEs) for skin and eye tissue when users, patients, and observers wear provided laser safety eyewear. Complies with ANSI Z136.1:2014, “American National Standard for Safe Use of Lasers”	N/A
10. Acoustic output measurement	Safety and effectiveness of OA/US probe	Complies with NEMA UD 2-2004 (R2009) Acoustic Output Measurement Standard for Diagnostic Ultrasound Equipment Revision 3	
11. Reliability/Functional Life Testing	System and components: • Laser • Optoacoustic (OA/US) • Probe, OA-16-1S • Medical Control Footswitch	2 million net laser shots with no hardware component failures, software failures, or laser emission failures	Pass

	• Power Control Module • Data Acquisition and Processing (DAP) Module • Modulo unit (Ultrasound) • AC Power Distribution Unit (PDU) • Mechanical componentry • Display (monitor and console)		
12. Reliability/Functional Life Testing, Mechanical Reliability	Functional testing of Entire system	No physical damage to the system	Pass
13. Reliability/Functional Life Testing	Functional testing of Footswitch pedal	Remain functional after >1887 press/release cycles	Pass
14. Reliability/Functional Life Testing, Extended Testing	Extended life testing of Entire system	2 million net laser shots with no hardware component failures, software failures, or laser emission failures	Pass
15. Risk management	Risk management associated with the Entire system	Complies with ISO 14971: 2007/(R)2010 (Corrected 4 October 2007) Medical devices - Application of risk management to medical devices	
16. Software verification and validation, per: • FDA Guidance document: Content of Premarket Submissions for Software Contained in Medical Devices, issued on May 2005 • FDA Guidance document: Off-The-Shelf Software Use in Medical Devices, issued on September 2019 • FDA Guidance document: General Principles of Software Validation, issued on January 2002 17. Cybersecurity per FDA Guidance document: Content of Premarket Submissions for Management of Cybersecurity in Medical Devices issued on October 2014	Testing Imagio Breast Imaging System software	Verification tests, software code reviews, unit testing, system level testing and defect tracking and dispositioning met all specifications.	Pass
	Testing SenoGram software	Verification included testing of the user interface, API, and computational components. Test results verified that the SenoGram software produced the expected outputs for valid and invalid inputs, edge cases, minimum values, and maximum values. Complies with ISO 14971: 2007/(R)2010 (Corrected 4 October 2007) Medical devices - Application of risk management to medical devices, ISO 13485 (2016) Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes, and IEC62304 Medical device Software (2006)	Pass
18. Packaging	Testing Imagio Breast Imaging System crate (Device is not supplied sterile)	The testing passed for protecting Imagio Breast Imaging System components during shipping.	Pass

19. Usability Testing/ Human Factors	Testing usability of entire system	Usability testing was conducted by sonographers and radiologists. Testing was performed according to human factors engineering standards: • AAMI/ANSI HE75:2009/(R) 2018 Human factors engineering – Design of medical devices • ANSI/AAMI/IEC 62366-1: 2015 Medical Devices-Part 1: Application of usability engineering to medical devices	Pass

A. Laboratory Studies/ Tissue Phantom Studies

Testing was conducted using various tissue-mimicking phantoms to assess device image quality and blood oxygenation measurement performance. Phantom testing was also used to demonstrate equivalent performance of the final device version against the previous device version used to collect original clinical study image data in the PINONEER study (please see summary of primary clinical study section below). Specific phantom tests were performed to evaluate: spatial resolution (axial, lateral, and elevational); geometric accuracy and precision; OA/US co-registration accuracy; image uniformity; depth of visualization; OA signal sensitivity, linearity, and dynamic range; vessel size measurement accuracy; oxygen saturation resolution and precision; out-of-plane absorber artifacts; and effects of laser energy variation on image quality and OA image colorization. Results showed that the device can detect blood vessel-mimicking targets in a breast-like background medium and map relative differences in blood oxygen saturation.

Table 2. Tissue Phantom Testing

Test	Purpose	Acceptance Criteria	Results
1. Spatial Resolution	Evaluate and quantify in-plane (axial, lateral), and out-of-plane (elevational) spatial resolution of OA images	None	Axial resolution, short wavelength = 0.58 ± 0.10 mm Axial resolution, long wavelength = 0.54 ± 0.10 mm Lateral resolution, short wavelength= 1.12 ± 0.35 mm Lateral resolution, long wavelength= 1.09 ± 0.25 mm Elevational resolution, short wavelength = 2.7 ± 0.4 mm (at ~4.5 mm depth), 5.6 ± 0.2 mm (at ~34 mm depth) respectively. Elevational resolution, long wavelength = 2.7 ± 0.4 mm (at ~4.5 mm depth), 5.4 ± 0.5 mm (at ~34.5 mm depth) respectively.
2. Geometric Accuracy and Precision	Evaluate accuracy of measured 1D distances and 2D areas in OA images. Assess OA image precision with repeated acquisitions.	None	Worst-case horizontal error = +0.81/-0.54 mm, std. deviation = 0.33 mm (over both wavelength) Worst-case vertical error = +0.19/-0.36 mm, std. deviation = 0.13 mm (over both wavelengths)

			Worst-case Image precision = +0.23 mm/-0.90 mm (over both wavelengths) Average percent errors of drawn ellipses were 0.4% in diameter, 0.7% in area, and 0.3% in circumference.
3. OA/US Co-Registration	Evaluate co-alignment of fused OA, US images	None	Worst-case horizontal error, -0.94/ +0.85 mm, std. deviation = 0.33 mm Worst-case vertical error = -0.17/ +0.21 mm, std. deviation = 0.09 mm (over both wavelengths)
4. Image uniformity	Quantify horizontal and vertical signal uniformity	None	With clinical contrast settings, Horizontal variation <2 dB (near-field) or <6 dB (far-field). Vertical uniformity < 31 dB (near-field), < 35 dB (far-field) due to expected effect of optical attenuation vs. depth.
5. Depth detection	Quantify the maximum penetration depth of OA imaging	None	Max imaging depth > 4 cm for OA Short and OA Long for detecting deoxygenated and oxygenated vessels, respectively.
6. Sensitivity-linearity	Evaluate and quantify OA sensitivity to and linearity vs. optical absorption	None	OA signal is highly linear vs. changes in target absorption coefficient using fixed contrast settings ($R^2 > 0.986$). Sensitivity = 0.046 cm^{-1}/grayscale for OA Short, 0.0343 cm^{-1}/grayscale for OA Long using fixed contrast settings. Clinical contrast settings can result in saturation effects, as expected.
7. OA Dynamic Range	Evaluate and quantify the OA dynamic range of the Imagio Breast Imaging System	None	OA dynamic range (OA Short): 9.079-22.976 dB OA dynamic range (OA Long): 10.015-23.923 dB
8. Accuracy of vessel diameters for simulated blood vessels	Evaluate accuracy of measuring tube diameters with the Imagio Breast Imaging System OA imaging	None	Device detects differences in vessel diameters correlated with known diameters, although measured diameter values are overestimated.
9. Oxygen saturation variation	Quantify the ability of the Imagio Breast Imaging System to depict and resolve differences in blood oxygen saturation	None	Device can detect SO_2 differences of ~3.5% ± 2.3% for targets near 100% SO_2, ~11% ± 15% for targets near 50% SO_2.
10. Out-of-plane absorber effects	Evaluate and quantify the effects of out-of-plane absorbers on the OA colorization	None	Out-of-plane absorber artifacts can potentially affect OA image colorization. Effects are stronger when out-of-plane target has similar SO_2 and smaller vessel diameter relative to in-plane target.
11. Dual wavelength laser energy variation	Quantify the effects of varying laser energy on image quality	None	Device maintains accurate colorization even with reduced laser energy beyond allowable tolerances for operation.

B. Animal Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a series of pivotal clinical studies to establish a reasonable assurance of safety and effectiveness of Imagio Breast Imaging System. Data from these clinical studies are the basis for the PMA approval decision. A summary of the clinical studies is presented below.

A. Study Design

The database for this PMA reflected data collected from December 2012 through September 2015 and included 1972 patients. There were 16 investigational sites, 7 academic and 9 private practices. All sites were in the United States of America (USA).

The applicant conducted a single arm, sequentially read, controlled, blinded, multi-reader, multi-case (MRMC) pivotal study, referred to as Reader-02, to establish a reasonable assurance of Imagio Breast Imaging System safety and effectiveness. The primary goal of the Reader-02 was to demonstrate that readers using the full functionality of Imagio (IUS+OA) performed better compared to when using IUS alone in terms of specificity at a fixed sensitivity of 98%. The images used in Reader-02 were a subset of the images acquired in a previous study called the PIONEER Study. PIONEER Study data collection is described next, followed by case selection for the Reader-02 Study, reader qualifications and training, and image interpretation procedures.

The Reader-02 Pivotal Study's endpoints were as follows:

Primary endpoint: Evaluate reader specificity with IUS alone at 98% sensitivity versus Imagio (IUS+OA) at the same sensitivity.

Secondary endpoints: Evaluate the following for IUS alone versus Imagio (IUS+OA):

a. Negative Likelihood Ratio (NLR) defined as ((1-sensitivity)/specificity)
b. Positive Likelihood Ratio (PLR) defined as (sensitivity/(1-specificity))
c. Partial Area Under the Receiver Operating Characteristics (ROC) Curve (pAUC) corresponding to 95-100% sensitivity

Sensitivity and specificity for the secondary endpoints were based on reader's POM scores with a positivity threshold of POM of 2%, i.e., POM>2% was considered a positive read (positive result) and POM≤2% was considered a negative read (negative result).

The evaluation used a sequential hierarchical approach for hypothesis testing, with secondary endpoints tested in the order NLR, PLR, and pAUC.

Corresponding Hypothesis testing were as follow:

Primary hypothesis test:
H0: $S_{Imagio} = S_{IUS}$ (no specificity [at 98% sensitivity] difference)
H1: $S_{Imagio} \neq S_{IUS}$ (superior specificity [at 98% sensitivity])
where S_{Imagio} and S_{IUS} represent specificity [at 98% sensitivity], values associated with Imagio (IUS + OA) and IUS.

Secondary hypothesis tests:
A 2% Probability of Malignancy (POM) cutoff was used as the positivity threshold. Specificity was defined as the proportion with a negative result (POM ≤2%) among all benign+TPB masses (to include all high-risk masses). Sensitivity was defined as the proportion with a positive result (POM >2%) among all malignant masses.

a. NLR:
   H0: $NLR_{IUS} = NLR_{Imagio}$ vs
   HA: $NLR_{IUS} \neq NLR_{Imagio}$ representing a reduction (improvement in NLR)

b. PLR:
   H0: $PLR_{IUS} = PLR_{Imagio}$ vs
   HA: $PLR_{IUS} \neq PLR_{Imagio}$ representing an increase (improvement in PLR)

c. Partial ROC AUC:
   H0: $pAUC_{IUS} = pAUC_{Imagio}$ vs
   HA: $pAUC_{IUS} \neq pAUC_{Imagio}$ representing an increase (improvement in partial ROC AUC)
   A sequential hierarchical approach for hypothesis testing was applied.

PIONEER Study Data Collection

Patient diagnostic images were obtained during the PIONEER study between December 2012 and September 2015.

The subjects for this Study were selected from women referred for a diagnostic breast ultrasound work-up who had a suspicious finding within the previous 45 business days, by palpation or by a screening mammogram or diagnostic methodology other than ultrasound, who were scheduled to undergo or already had a Clinical Diagnostic Ultrasound (CDU). The CDU at the time of Study enrollment was used to classify subjects as NDU (Negative Diagnostic Ultrasound) (CDU BI-RADS 3) or PDU (Positive Diagnostic Ultrasound) (CDU BI-RADS ≥4a) to determine if follow-up (NDU patients) or biopsy (PDU patients) was required.

The goal was to enroll ≥1,000 benign masses either with a benign biopsy or followed for a year with ≤20% increase in maximum diameter and no change in BI-RADS classification from 3 to 4a+.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria
Enrollment in the PIONEER study was limited to patients who met the following inclusion criteria (all conditions are to be met to be included in the study):

a. Has signed and dated informed consent, prior to initiation of any Study activities.
b. Has had an undiagnosed suspicious finding within the previous 45 business days, by palpation or by a screening or diagnostic methodology other than ultrasound; this may have included more than one suspicious mass.
c. Has at least 1 or up to 3 pre-selected and undiagnosed breast masses including suspicious solid masses and/or complex cystic and solid masses that the investigator had characterized as either BI-RADS 3, BI-RADS 4, or BI-RADS 5 that have been scheduled for either biopsy or follow-up.
d. Has at least one undiagnosed breast mass that was detected by one of the following 4 methodologies within 45 business days prior to enrollment with imaging results available for Study utilization:
    - Call backs for additional evaluation of suspicious area(s) identified by imaging other than ultrasound.
    - Diagnostic referral to assess focal physical symptoms and/or signs that were either a chief complaint of the subject or were elicited by the healthcare practitioner (excluding focal breast pain in the absence of other positive clinical findings).
    - Interval clinical problems (symptoms or physical findings, excluding isolated focal breast pain, that had developed between yearly mammograms).
    - Other referrals to CDU including subjects younger than 30 years old for a clinically suspicious area, or subjects referred from a screening Magnetic resonance imaging (MRI) because of an abnormality.
e. Is at least 18 years of age.
f. Has received a recommendation to either biopsy or not biopsy.
g. Is willing and able to comply with protocol required procedures.

Exclusion Criteria
Patients were not permitted to enroll in the PIONEER study if they met any of the following exclusion criteria (any condition by itself is sufficient to exclude a subject):

a. Subject is male.
b. Has a condition or impediment which could interfere with the intended field-of- view (i.e., breast implants within the previous 12 months, or tattoos).

c. Has or has had cancer in the ipsilateral breast or prior breast surgeries in the same quadrant of the ipsilateral breast that would have interfered with the ability to capture or interpret images.
d. Prior benign excisional breast biopsy within the immediate vicinity of the currently evaluated suspicious mass within the past 18 months (benign excisional biopsy not within immediate Imagio field-of-view will not exclude the subject from the Study).
e. Has greater than 3 suspicious masses.
f. Mass(es) of interest is greater than 4 cm.
g. Has all mass(es) characterized as BI-RADS 1 and/or 2 as determined using a CDU.
h. Currently has mastitis.
i. Has focal pain without thickening or mass.
j. Is pregnant or lactating.
k. Has open sores including insect bites, rash, poison ivy, and chafing on the skin of the ipsilateral breast.
l. Has an acute or a chronic hematoma and/or acute ecchymosis of the ipsilateral breast.
m. Is experiencing photo-toxicity associated with currently taking, or having taken, photosensitizing agents within the previous 72 hours such as sulfonamides, ampicillin, tetracycline. Is currently undergoing phototherapy.
n. Has a history of any photosensitive disease (e.g., porphyria, lupus erythematosus) or undergoing treatment for a photosensitive disease and was experiencing photosensitivity.
o. Concurrent neoadjuvant therapy prior to the Imagio evaluation or the biopsy.
p. Has previously had image guided core biopsy, image guided Directional Vacuum Assisted Biopsy (DVAB), or surgical biopsy of the mass of interest.
q. Has nipple rings that cannot be removed or are not removed during Imagio evaluation.

2. Methodology

Subjects were prospectively enrolled upon confirmation of being BI-RADS 3, BI-RADS 4, or BI-RADS 5, as confirmed by CDU evaluation of the suspicious mass(es). Subjects who had all mass(es) characterized as BI-RADS 1 and/or 2 as determined using a CDU were regarded as screen failures, as shown in Figure 4 below. Of the remaining subjects who consented (n=2105), 23 were considered as enrollment failures because (1) mass was too deep for Imagio™ to visualize, or (2) device malfunctioned prior to or during the scanning procedure, or (3) subject was withdrawn prior to scanning procedure initiated. Remaining subjects (n=2082) were exposed to OA.

First 10 subjects scanned at the Cancer Therapy and Research Center (CTRC) and the next 100 subjects enrolled as pilot cases for the study were excluded from the Safety Population of the study. The PIONEER Safety Population thus consisted of 1972 subjects.

Subjects were scheduled for an Imagio procedure after the decision whether to biopsy was made, but prior to any biopsy. The subjects must have had the Imagio procedure within 10 days of the enrollment visit and within 45 business days before the biopsy. Subjects in the NDU group who opted not to undergo a biopsy were to have a second Imagio™ procedure 12 months (± 30 days) after the initial imaging procedure.

All images, both OA and IUS, were to undergo QA review by the quality assurance radiologists (QARs). To ensure image reading consistency, the assessment of all Study imaging, including OA, was managed by an independent Imaging Core Laboratory (ICL).

Starting with the PIONEER Safety Population, 233 subjects were excluded from the PIONEER Intent-to-Diagnose (ITD) Population for the following reasons: QA failure of images, technical failures, PDU with no biopsy, NDU with no truth panel review, and protocol deviations.

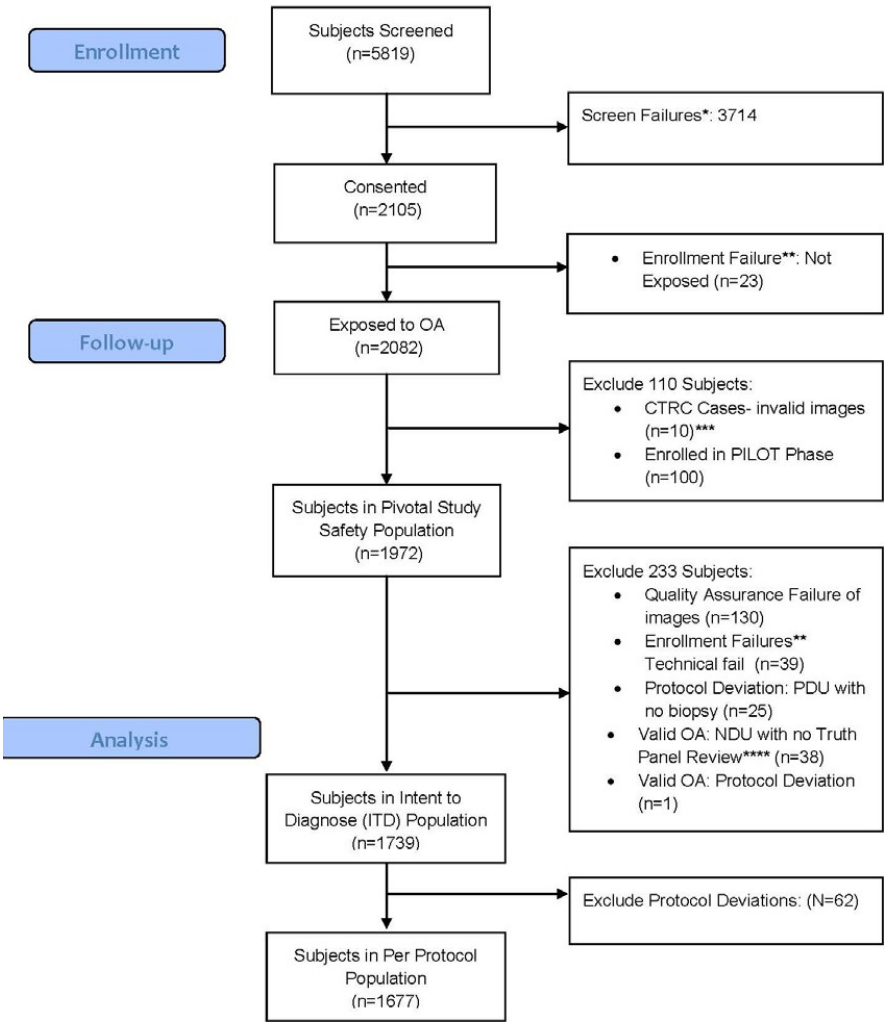

Figure 4 - Study Accountability Flowchart - Disposition By Subject

3. Ground truth determination

For masses that underwent biopsy, the final diagnosis depended on the histopathological examination of the biopsy data from the suspected mass by an independent central histopathologist. Samples determined by the central histopathologist to be high-risk (HR), such as atypical ductal hyperplasia, atypical lobular neoplasia, and lobular carcinoma in situ were considered to be benign in the study effectiveness analysis. A Truth Panel was established to review and/or adjudicate NDU cases with follow-up at 12 months (≥11 months) to determine if the cases were True Negative (Truth Panel Benign [TPB]). TPB was determined for subjects who had masses classified as BI-RADS 3 with CDU by site investigators that were not biopsied and had ≤20% increase in max diameter and no change in BI-RADS classification from 3 to 4a+ at the 12-month follow up. Panel members evaluated available imaging modalities in the following order: CDU, mammography, MRI and IUS. OA was not utilized for this determination. NDU subjects who were not biopsied within the 12-month follow-up window and showed an increase in mass size (>20%) or a BI-RADS change to >3 were classified as truth panel change (TPC) masses by the Truth Panel. There were 8 such TPC masses, all of which were BI-RADS 3 by CDU at 12-month follow-up; none were recommended for biopsy by site investigators. The PIONEER ITD Population included 1739 subjects with a total of 652 biopsied cancer, 41 biopsied high risk, and 848 biopsied benign. 190 non-biopsied TPB (truth panel benign) and 8 non-biopsied "other" (truth panel change or TPC) masses. PIONEER ITD **analysis** population excluded the 8 TPC cases because they could not be classified as TPB, high-risk, or cancer.

Case Selection for Reader-02 Pivotal Study

The applicant conducted an initial MRMC reader study using the cases in the PIONEER ITD Population. Due to methodological issues, the applicant was not able to complete the submission of the final results from this study to the FDA. Subsequently, the applicant conducted the Reader-02 Pivotal Study, which used a subset of the images acquired for the PIONEER Pivotal Study to support their current PMA application. No new subjects were enrolled for Reader-02 Study. The patient population for Reader-02 Study is described in the following.

Masses were selected at random for the Reader-02 Study in proportion to the original assignment distribution of BI-RADS classifications among subjects in the PIONEER Study by conventional diagnostic ultrasound (CDU). Masses selected from the PIONEER ITD analysis population for the Reader-02 Study could include up to 7 blocks of 120 images. The Reader-02 Pivotal Study thus consisted of between 480 to 840 masses with complete imaging read sets from the original PIONEER ITD analysis population. The data were organized and presented to readers in blocks of 120 masses, each consisting of 72 benign plus 3 high risk (to be categorized as benign) and 45 malignant masses (reflecting a similar prevalence of cancer as the overall PIONEER ITD analysis population, approximately 38%). To facilitate the

alignment of the PIONEER Pivotal Study data with the Reader-02 Pivotal Study data in terms of mammogram availability, the mass image set sampling plan selected a benign mass proportion with and without mammograms depending on availability of the mammograms to be the same as in PIONEER; this stratification did not apply for malignant masses where nearly all masses were previously evaluated using mammography**.**

The number of masses was 480 masses in total, comprised of the following:

- 180 malignant masses
- 300 benign masses (288 benign, 12 high risk defined as atypical ductal hyperplasia, atypical lobular neoplasia, and lobular carcinoma in situ, etc.)

A total of 480 complete read sets (4 blocks of 120 read sets each) from the original PIONEER ITD **analysis** population were randomly selected with stratification in accordance with the Reader-02 Pivotal Study Sampling Plan from within the previous PIONEER Pivotal Study. Sample size was assessed at a blinded interim analysis after the first 360 reads and could be adjusted as necessary based on inter- and intra-reader variance up to a maximum of 840 reads. To avoid any potential for bias, all four blocks had been read by all readers in advance of the database lock for the pre-planned interim analysis.

Mass Inclusion and Exclusion Criteria

The mass inclusion criteria for the Reader-02 Pivotal Study were as follows:

a. One analyzable mass per patient: BI-RADS 3, 4a, 4b, 4c and 5 masses as declared by clinical site investigator via PIONEER study inclusion criteria and categorized as BI-RADS 3, 4a, 4b, 4c, and 5 by CDU
b. Masses declared to be in the PIONEER ITD analysis population, including high risk cases per original PIONEER protocol
c. Patient age, indication for study entry and available medical history
d. Evaluable mammograms (when available) and IUS and OA video loops and still images for each mass

The mass Exclusion criteria for the Reader-02 Pivotal Study were as follows:

a. Critical missing IUS or OA still image and/or video loop views or incorrect IUS or OA stills and video loops that would preclude a case from being evaluated by readers
b. Reader-02 proficiency test and training cases
c. Failure of quality assurance review, as described below.

Quality Assurance Review

The quality assurance radiologists (QARs) were two physicians selected by Seno Medical with knowledge and experience in breast imaging. In addition to exam quality checks, the QAR's role was to identify and label, with guidance from limited medical history data and breast MRI and CDU exams, the appropriate intent-to-

diagnose mass on mammogram and IUS and Imagio (IUS+OA) exams to be read and scored by the 15 independent readers on this study.

Reader Qualifications and Training

The study included 15 readers with an additional 5 back-up readers depending on qualifications and availability. Readers that participated in any previous study were not eligible to participate as independent readers in this Reader-02 Pivotal Study. Only readers who met the following requirements were allowed to read images for this study:

a. Completed residency and are board certified in radiology
b. Active breast imager for at least 3 years.
c. Readers to meet mammography interpretation requirements per Mammograph quality Standards ACT (MQSA) for the year prior to study
d. Readers to meet diagnostic ultrasound interpretation requirements per American College of Radiology (ACR) for year prior to study
e. For the clinical study, a willingness to use BI-RADS 4 sub-categories
f. For the clinical study, the ability to participate and read all masses in both IUS and IUS+OA reader sessions

The readers were required to undergo training before they were permitted to participate in the Reader-02 Pivotal Study. Training consisted of three modules: Didactic training, interactive reading, and test. Didactic training included fundamentals of OA, OA feature scoring, correlation of OA features with core biopsy histopathology, OA artifacts, IUS feature scoring, Seno learnings from previous studies, and the use of the SenoGram. In the interactive reading module, the readers read and scored a mixture of up to 30 malignant and benign cases after being trained on how to use a reading station, draw regions of interest (ROIs), score IUS and OA features, use the SenoGram to aid in predicting OA POM and BI-RADS category. In the test module, the readers had to pass a proficiency test involving the scoring and interpretation of 30 cases before starting their study reads. If this was not achieved the first time, then the reader took the test a second time. The reader was given remediation training targeted to the masses for which they made errors within the first 30 case test set, and the reader was given a second opportunity to take the test on a different set of 30 test cases. If a reader failed the second test, remediation again took place before they started the Reader-02 Pivotal Study reads. The reader proceeded to read Reader-02 pivotal cases whether or not they passed the second test.

Image Interpretation

Interpretation of each case consisted of two consecutive reads: Read 1, immediately followed by Read 2 within the same reading session. In both Read 1 and Read 2, the radiologist provided a POM rating between 0 and 100 using a custom graphical interface with zoomed-in gradations at low probabilities (POM<2%), and a corresponding BI-RADS score (BI-RADS 2, 3, 4a, 4b, 4c or 5).

Read 1 reflected the typical information available to a radiologist when evaluating standard ultrasound images, taking into consideration the mass, patient history and assessing mammogram BI-RADS results, when available. Read 1 (IUS reads) served as the control representing current clinical practice.

- Read 1:
    - Data provided for the reader: Patient History (age) + Mammogram (if available) + IUS (stills and videos provided).
    - Reader output: IUS Probability of Malignancy (POM) and BI-RADS category assigned in the data form, then locked.

Read 2 displayed the OA images in addition to the data provided in Read 1. Each reader entered 5 feature scores for IUS, 5 feature scores for OA, and four other features (patient age, mass size, depth to the posterior aspect of the mass and mammographic BI-RADS classification) into the SenoGram report form. Based on this information, the SenoGram displayed a predicted Likelihood of Malignancy (LOM) computed from reader input. Each reader then assigned final POM and BI-RADS scores.

- Read 2:
    - Data initially provided for the reader: Patient History (age) + Mammogram (if available) + IUS (stills and videos provided), and Imagio (IUS+OA) (stills and videos provided).
    - Input provided by the reader to SenoGram: 5 feature scores for IUS, 5 feature scores for OA, and four other features.
    - Reader output: Imagio (IUS+OA) POM and BI-RADS category after viewing the SenoGram output. The data form is then locked.

4. Follow-up Schedule

All Negative Diagnostic Ultrasound (NDU) patients not undergoing a biopsy were scheduled to return for follow-up examinations with an OA and IUS procedure at 12-month (±30 days) after the initial imaging procedure to determine True Negative status of subjects by the Truth Panel.

Prior to enrollment, subjects for this study had a suspicious finding within the previous 45 business days, by palpation or by a screening mammogram or diagnostic methodology other than ultrasound, and the subjects were scheduled to undergo or already had a CDU as per the site best practice guidelines. Once enrolled, patient medical history, breast mass history, and mass pathology data were recorded. Adverse Events were recorded for all patients at baseline and at 12-month Imagio visits.

B. Study Population Demographics and Baseline Parameters

Demographic and baseline characteristics of the PIONEER subjects whose masses/images were used in the Reader-02 study are presented in Table 3. Of the 480 masses read in the Reader-02 study, the overall mean age was 49.9±14.4 years; in the benign+TPB+HR group, the mean was 44.2±12.5 years, and in the malignant group it was 59.4±12.2 years, consistent with the age distribution of cancer diagnosis in the population. Almost ninety percent (89.6%) of subjects had available mammography, of which 84.0% were benign+TPB+HR subjects and 98.9% were cancer subjects.

In the overall ITD population, two (0.4%) had CDU BI-RADS scores of 2; 74 (15.4%) were score 3; 129 (26.9%) were score 4a, 84 (17.5%) were score 4b, 87 (18.1%) were score 4c, and 102 (21.3%) were score 5. As expected, a greater proportion of subjects in the malignant group were scored BI-RADS 5 (96, 53.3%). Almost three-quarters of the masses (355, 74%) had a mammographic breast density of 2 or 3; 210 masses (43.8%) were palpable, and 199 masses (41.5%) were not. Almost half the subjects (219, 45.6%) were post-menopausal, and 14 (2.9%) had breast implants.

Table 3. Baseline Clinical Characteristics, Reader-02 Population

		Overall (N=480)	Benign+TPB+High Risk (N=300)	Cancer (N=180)
Mammography Present [n (%)]	Yes	430 (89.6)	252 (84.0)	178 (98.9)
	No	50 (10.4)	48 (16.0)	2 (1.1)
CDU BI-RADS [n (%)]	2 [1]	2 (0.4)	2 (0.7)	0
	3	74 (15.4)	73 (24.3)	1 (0.6)
	4a	129 (26.9)	125 (41.7)	4 (2.2)
	4b	84 (17.5)	70 (23.3)	14 (7.8)
	4c	87 (18.1)	22 (7.3)	65 (36.1)
	5	102 (21.3)	6 (2.0)	96 (53.3)
	Missing [1]	2 (0.4)	2 (0.7)	0
Breast Density [n (%)]	1	24 (5.0)	10 (3.3)	14 (7.8)
	2	168 (35.0)	93 (31.0)	75 (41.7)
	3	187 (39.0)	116 (38.7)	71 (39.4)
	4	40 (8.3)	26 (8.7)	14 (7.8)
	Missing	61 (12.7)	55 (18.3)	6 (3.3)
Palpable [n (%)]	Yes	210 (43.8)	121 (40.3)	89 (49.4)
	No	199 (41.5)	130 (43.3)	69 (38.3)
	Unknown	71 (14.8)	49 (16.3)	22 (12.2)
Implants [n (%)]	Yes	14 (2.9)	8 (2.7)	6 (3.3)
	No	466 (97.1)	292 (97.3)	174 (96.7)
Post Menopausal [n (%)]	Yes	219 (45.6)	90 (30.0)	129 (71.7)
	No	258 (53.8)	208 (69.3)	50 (27.8)

	Missing	3 (0.6)	2 (0.7)	1 (0.6)
Any Relevant Medical History [n (%)]	Yes	245 (51.0)	136 (45.3)	109 (60.6)
	No	235 (49.0)	164 (54.7)	71 (39.4)
Age	N	480	300	180
	Mean	49.9	44.2	59.4
	Median	49.0	45.0	59.5
	Std Dev	14.4	12.5	12.2
		Overall (N=480)	**Benign+TPB+High Risk (N=300)**	**Cancer (N=180)**
Site [n (%)]	Min, Max	18, 88	18, 77	28, 88
	95% CI	(48.6, 51.2)	(42.8, 45.6)	(57.6, 61.2)
	1	43 (9.0)	33 (11.0)	10 (5.6)
	2	28 (5.8)	16 (5.3)	12 (6.7)
	3	18 (3.8)	10 (3.3)	8 (4.4)
	4	69 (14.4)	40 (13.3)	29 (16.1)
	5	18 (3.8)	9 (3.0)	9 (5.0)
	6	31 (6.5)	6 (2.0)	25 (13.9)
	7	16 (3.3)	13 (4.3)	3 (1.7)
	8	55 (11.5)	41 (13.7)	14 (7.8)
	9	9 (1.9)	9 (3.0)	0
	10	6 (1.3)	6 (2.0)	0
	11	22 (4.6)	15 (5.0)	7 (3.9)
	12	46 (9.6)	24 (8.0)	22 (12.2)
	13	27 (5.6)	12 (4.0)	15 (8.3)
	14	58 (12.1)	38 (12.7)	20 (11.1)
	15	16 (3.3)	14 (4.7)	2 (1.1)
	16	18 (3.8)	14 (4.7)	4 (2.2)

CDU = Conventional Diagnostic Ultrasound; BI-RADS = Breast Imaging-Reporting and Data System; TPB = Truth Panel benign

The depth to the posterior margin of the mass was measured by the Reader-02 readers during their evaluations. These data for the Reader-02 population for all readers are presented in Table 4. On average masses were 1.73±0.65 cm from the chest wall to the posterior margin of the mass with a range from 0.47 cm to 3.77 cm.

Table 4: Clinical Characteristics – Depth to Posterior Margin of Mass (cm), Reader-02 Population, All Readers

	Overall (N=480)	**Benign+TPB+High Risk (N=300)**	**Cancer (N=180)**
Mean	1.735	1.605	1.951
Median	1.667	1.553	1.927
Std Dev	0.6528	0.6155	0.6578
Min, Max	0.47, 3.77	0.47, 3.64	0.55, 3.77
95% CI	(1.676, 1.793)	(1.535, 1.675)	(1.854, 2.047)

TPB = Truth Panel benign

Similarly, mass size was measured by the Reader-02 readers during their evaluations. These data for the Reader-02 population for all readers are presented in Table 5. On average masses were 1.45±0.77 cm in diameter with a range from 0.33 cm to 3.89cm.

Table 5: Clinical Characteristics – Mass Size (cm), Reader-02 Population, All Readers

	Overall (N=480)	Benign+TPB+High Risk (N=300)	Cancer (N=180)
Mean	1.452	1.413	1.516
Median	1.267	1.230	1.283
Std Dev	0.7730	0.7504	0.8073
Min, Max	0.33, 3.89	0.33, 3.89	0.39, 3.89
95% CI	(1.383, 1.521)	(1.328, 1.499)	(1.397, 1.635)

TPB = Truth Panel benign

Of the 497 cases presented for Quality Assurance Radiologist (QAR) review, 17 cases failed. The reasons for QAR review failure were (1) A mammogram-present subject that, after QAR review, had no mammograms that were acceptable to display (N=14), and (2) QAR could not confirm subject age as presented on medical history data across one or more read exams (N=4). One case failed for both of these reasons. No case failed because the mass could not be marked on IUS or OA. The diagnosis (malignant vs. benign+TPB+high risk) for masses that passed the Quality Assurance Radiologist (QAR) review was compared to those that failed (Table 6).

Table 6: Diagnosis for Masses, QAR Pass versus QAR Fail

Parameter	Overall (N=497)	QAR Pass (N=480)	QAR Fail (N=17)
Final Diagnosis [n (%)]			
Cancer	187 (37.6)	180 (37.5)	7 (41.2)
Benign + TPB + High Risk	310 (62.4)	300 (62.5)	10 (58.8)

QAR = Quality Assurance Radiologist; TPB = Truth Panel benign

C. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the PIONEER Safety cohort of 1972 patients. The key safety outcomes for this study are presented and adverse effects are reported below in Tables 7 to 12.

Adverse effects that occurred in the PMA clinical study:

As shown in Table 7, overall, 52 subjects (2.6%) in the PIONEER Safety Population experienced an Adverse Event (AE). Forty subjects (2.0%) experienced at least one AE assessed as mild and 11 subjects (0.6%) experienced at least one AE assessed as moderate in severity. One subject (0.1%) reported two AEs assessed as severe and serious. This subject experienced atrial fibrillation and congestive heart failure, both assessed as serious, severe, and not related to the procedure. The event of atrial fibrillation was attributed to renal failure and the event of congestive heart failure was attributed to atrial fibrillation.

The most common AEs by system organ class were injury, poisoning, and procedural complications (21 events) followed by nervous system disorders (16 events). The most common events by preferred term (PT) were paraesthesia (10

events) and post procedural hematoma (all post-biopsy; 5 events). Twenty-five events, including 10 events of paraesthesia, had a start date of the same day as the OA procedure.

Of the 7 Serious Adverse Events (SAE(s)) reported in 5 subjects, none were considered related to the OA procedure. There were no serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs) or deaths reported during the Study.

Of the 52 subjects with AEs, 10 subjects (0.5%) reported 11 events that were considered related (possibly, probably, likely) to the OA procedure (Table 8). All 11 procedure-related AEs were considered mild.

A single event of "burns second degree" occurred. This patient had a moderate skin rash of undetermined origin. This was deemed by the sponsor to be more likely due to contact dermatitis with post-biopsy tape than a photothermal skin injury due to laser exposure.

Table 7: Overall Summary of Adverse Events, Safety Population, PIONEER Pivotal Study

			Biopsy			No Biopsy	
Parameter (Counts by Subject) [n(%)]	**Overall (N=1972)**	**Benign + TPB (N=1115)**	**Cancer (N=692)**	**High Risk (N=43)**	**Benign (N=925)**	**TPB (N=190)**	**Other (N=122)**
At least one AE	52 (2.6)	32 (2.9)	13 (1.9)	0	16 (1.7)	16 (8.4)	7 (5.7)
At least one AE on OA Procedure date	22 (1.1)	11 (1.0)	9 (1.3)	0	10 (1.1)	1 (0.5)	2 (1.6)
AEs by worst severity							
Mild	40 (2.0)	23 (2.1)	12 (1.7)	0	15 (1.6)	8 (4.2)	5 (4.1)
Moderate	11 (0.6)	8 (0.7)	1 (0.1)	0	1 (0.1)	7 (3.7)	2 (1.6)
Severe	1 (0.1)	1 (0.1)	0	0	0	1 (0.5)	0
At least one OA Procedure-related AE	10 (0.5)	5 (0.4)	4 (0.6)	0	4 (0.4)	1 (0.5)	1 (0.8)
Procedure-related AEs by worst relationship							
Not related	42 (2.1)	27 (2.4)	9 (1.3)	0	12 (1.3)	15 (7.9)	6 (4.9)
Possibly	5 (0.3)	2 (0.2)	2 (0.3)	0	2 (0.2)	0	1 (0.8)
Probably	1 (0.1)	1 (0.1)	0	0	1 (0.1)	0	0
Likely	4 (0.2)	2 (0.2)	2 (0.3)	0	1 (0.1)	1 (0.5)	0
Procedure-related AEs by worst severity							
Mild	10 (0.5)	5 (0.4)	4 (0.6)	0	4 (0.4)	1 (0.5)	1 (0.8)
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
At least one SAE	5 (0.3)	4 (0.4)	0	0	1 (0.1)	3 (1.6)	1 (0.8)
At least one OA Procedure-related SAE	0	0	0	0	0	0	0
UADEs	0	0	0	0	0	0	0
SADEs	0	0	0	0	0	0	0

AE = Adverse event; OA = Opto-acoustic; PDUNB = Positive diagnostic ultrasound, no biopsy SADE = Serious adverse device effect; SAE = Serious adverse event; TP = Truth Panel; TPB = Truth Panel benign; TPC = Truth Panel change; TPND =

Negative diagnostic ultrasound (NDU) masses with no biopsy and no Truth Panel result; UADE = Unanticipated adverse device effect. Note: Other includes TPC, TPND and PDUNB.

Table 8: Summary of OA Procedure-Related Adverse Events, Safety Population, PIONEER Pivotal Study

	Overall	
SYSTEM ORGAN CLASS **Preferred Term**	**N (%) of Subjects**	**N of Events**
Total OA Procedure-Related AEs	10 (0.5)	11
NERVOUS SYSTEM DISORDERS	7 (0.4)	7
Paraesthesia	7 (0.4)	7
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.1)	2
Burns Second Degree	1 (0.1)	1
Procedural Pain	1 (0.1)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.1)	2
Erythema	1 (0.1)	1
Skin Warm	1 (0.1)	1

AE = adverse event; OA = Optoacoustic.

Relevant safety data are summarized here from the PIONEER dataset for the 480 subjects who contributed masses to the Reader-02 Pivotal Study.

Of the 480 subjects who contributed masses for reading in the Reader-02 study, 16 (3.3%) experienced at least one AE during the study, of which 6 (1.3%) occurred on the date of the Imagio procedure (Table 9). Three subjects (0.6%) had at least one Imagio procedure-related AE. There were no AEs that were graded as severe; 14 (2.9%) were considered mild and two (0.4%) were graded moderate. All Imagio procedure-related AEs were considered mild. Two subjects (0.4%) experienced a serious adverse event (SAE), neither of which was Imagio procedure-related; one experienced rupture of a saline breast implant, requiring revision surgery, and one was diagnosed with Stage I non-small cell lung cancer and underwent resection of the affected lobe in the right lung. There were no SADE or UADE.

Table 9: Summary of Adverse Events, Reader-02 Population

			Biopsy			**No Biopsy**
Parameter (Counts by Subject)	**Overall (N=480)**	**Benign + TPB + HR (N=300)**	**Cancer (N=180)**	**High Risk (N=12)**	**Benign (N=237)**	**TPB (N=51)**
At least one AE [n (%)]	16 (3.3)	12 (4.0)	4 (2.2)	0	7 (3.0)	5 (9.8)
At least one AE on OA Procedure date [n (%)]	6 (1.3)	4 (1.3)	2 (1.1)	0	3 (1.3)	1 (2.0)
At least one OA Procedure-related AE [n (%)]	3 (0.6)	2 (0.7)	1 (0.6)	0	1 (0.4)	1 (2.0)
AEs by worst relationship [n (%)]						
Not related	13 (2.7)	10 (3.3)	3 (1.7)	0	6 (2.5)	4 (7.8)
Possibly	0	0	0	0	0	0
Probably	0	0	0	0	0	0
Likely	3 (0.6)	2 (0.7)	1 (0.6)	0	1 (0.4)	1 (2.0)
AEs by worst severity [n (%)]						
Mild	14 (2.9)	10 (3.3)	4 (2.2)	0	7 (3.0)	3 (5.9)

Moderate	2 (0.4)	2 (0.7)	0	0	0	2 (3.9)
Severe	0	0	0	0	0	0
OA Procedure-related AEs by worst severity [n(%)]						
Mild	3 (0.6)	2 (0.7)	1 (0.6)	0	1 (0.4)	1 (2.0)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
At least one SAE [n(%)]	2 (0.4)	2 (0.7)	0	0	1 (0.4)	1 (2.0)
At least one OA Procedure-related SAE [n(%)]	0	0	0	0	0	0
Serious Adverse Device Effect [n(%)]	0	0	0	0	0	0
Unanticipated Adverse Device Effect [n(%)]	0	0	0	0	0	0

TPB = Truth Panel benign; HR = High Risk; AE = Adverse Event; SAE = Serious Adverse Event; OA = Optoacoustic (Imagio breast Imaging System)

Table 10 summarizes all AEs by system organ class (SOC) and preferred term (PT). There were no individual AEs that occurred at a rate of more than 1% in the overall cohort of 480 masses. Paraesthesia was the highest occurring AE with five subjects (1.0%) experiencing this event, four (1.3%) in the benign+TPB+HR group and one (0.6%) in the malignant group. All other AEs were a single instance.

Table 10: Adverse Events by SOC and PT, Reader-02 Population

					Biopsy						**No Biopsy**	
	Overall (N=480)		**Benign + TPB+ HR (N=300)**		**Cancer (N=180)**		**High Risk (N=12)**		**Benign (N=237)**		**TPB (N=51)**	
SYSTEM ORGAN CLASS Preferred Term	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events
Total Subjects with Any AE	16 (3.3)	19	12 (4.0)	14	4 (2.2)	5	0	0	7 (3.0)	7	5 (9.8)	7
NERVOUS SYSTEM DISORDERS	5 (1.0)	5	4 (1.3)	4	1 (0.6)	1	0	0	3 (1.3)	3	1 (2.0)	1
Paraesthesia	5 (1.0)	5	4 (1.3)	4	1 (0.6)	1	0	0	3 (1.3)	3	1 (2.0)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.8)	4	3 (1.0)	3	1 (0.6)	1	0	0	2 (0.8)	2	1 (2.0)	1
Contusion	1 (0.2)	1	1 (0.3)	1	0	0	0	0	1 (0.4)	1	0	0
Post Procedural Hematoma	1 (0.2)	1	1 (0.3)	1	0	0	0	0	1 (0.4)	1	0	0
Procedural Dizziness	1 (0.2)	1	0	0	1 (0.6)	1	0	0	0	0	0	0
Upper Limb Fracture	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
INFECTIONS AND INFESTATIONS	1 (0.2)	2	0	0	1 (0.6)	2	0	0	0	0	0	0
Postoperative Wound Infection	1 (0.2)	2	0	0	1 (0.6)	2	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.4)	2	2 (0.7)	2	0	0	0	0	1 (0.4)	1	1 (2.0)	1
Dermatitis Contact	1 (0.2)	1	1 (0.3)	1	0	0	0	0	1 (0.4)	1	0	0
Skin Warm	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
CARDIAC DISORDERS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1

Tachycardia	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	1 (0.4)	1	0	0
Device Breakage	1 (0.2)	1	1 (0.3)	1	0	0	0	0	1 (0.4)	1	0	0
HEPATOBILIARY DISORDERS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
Gallbladder Disorder	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.2)	1	0	0	1 (0.6)	1	0	0	0	0	0	0
Muscle Spasms	1 (0.2)	1	0	0	1 (0.6)	1	0	0	0	0	0	0

SOC = System Organ Class; PT = Preferred Term; TPB = Truth Panel benign; HR = High Risk; AE = Adverse Event; OA = Optoacoustic (Imagio Breast Imaging System)

Table 11 summarizes Imagio procedure-related AEs by SOC and PT. There was a total of three subjects (0.6%) with one or more Imagio procedure-related AEs. Three subjects (0.6%) experienced paraesthesia, and one (0.2%) of the three subjects also experienced skin warming.

Table11: Imagio Procedure-Related Adverse Events by SOC and PT, Reader-02 Population

					Biopsy						**No Biopsy**	
	Overall (N=480)		**Benign + TPB + HR (N=300)**		**Cancer (N=180)**		**High Risk (N=12)**		**Benign (N=237)**		**TPB (N=51)**	
SYSTEM ORGAN CLASS Preferred Term	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events
Total Subjects with OA Procedure- Related AE	3 (0.6)	4	2 (0.7)	3	1 (0.6)	1	0	0	1 (0.4)	1	1 (2.0)	2
NERVOUS SYSTEM DISORDERS	3 (0.6)	3	2 (0.7)	2	1 (0.6)	1	0	0	1 (0.4)	1	1 (2.0)	1
Paraesthesia	3 (0.6)	3	2 (0.7)	2	1 (0.6)	1	0	0	1 (0.4)	1	1 (2.0)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
Skin Warm	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1

SOC = System Organ Class; PT = Preferred Term; TPB = Truth Panel benign; HR = High Risk; AE = Adverse Event; OA = Optoacoustic (Imagio Breast Imaging System)

Table 12 summarizes AEs occurring on the Imagio Breast Imaging System procedure date by SOC and PT. A total of six subjects (1.3%) experienced one or more AEs on the Imagio Breast Imaging System procedure date, of which five (1.0%) were paraesthesia. There were also single instances (0.2% each) of tachycardia, procedural dizziness and skin warming.

Table 12: Adverse Events Occurring on Imagio Procedure Date by SOC and PT, Reader-02 Population

					Biopsy						No Biopsy	
	Overall (N=480)		**Benign + TPB + HR (N=300)**		**Cancer (N=180)**		**High Risk (N=12)**		**Benign (N=237)**		**TPB (N=51)**	
SYSTEM ORGAN CLASS Preferred Term	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events	N(%) of Subjects	N of Events
Total Subjects with AE on OA Procedure Date	6 (1.3)	8	4 (1.3)	6	2 (1.1)	2	0	0	3 (1.3)	3	1 (2.0)	3
NERVOUS SYSTEM DISORDERS	5 (1.0)	5	4 (1.3)	4	1 (0.6)	1	0	0	3 (1.3)	3	1 (2.0)	1
Paraesthesia	5 (1.0)	5	4 (1.3)	4	1 (0.6)	1	0	0	3 (1.3)	3	1 (2.0)	1
CARDIAC DISORDERS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
Tachycardia	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.2)	1	0	0	1 (0.6)	1	0	0	0	0	0	0
Procedural Dizziness	1 (0.2)	1	0	0	1 (0.6)	1	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1
Skin Warm	1 (0.2)	1	1 (0.3)	1	0	0	0	0	0	0	1 (2.0)	1

SOC = System Organ Class; PT = Preferred Term; TPB = Truth Panel benign; HR = High Risk; AE = Adverse Event; OA = Optoacoustic (Imagio Breast Imaging System)

2. Effectiveness Results

The analysis of effectiveness was based on the 480 evaluable patients used within the Reader-02 study. As mentioned above, this study is a subset of the original PIONEER study which was completed on an ITD population of 1972 patients. Key effectiveness outcomes are presented below.

The Reader-02 Pivotal Study met its primary endpoint and demonstrated that Imagio Breast Imaging System has better specificity than IUS at fixed sensitivity of 98%.

Specificity at a fixed sensitivity of 98% (fSp) and partial area under the ROC curve (pAUC) between sensitivities of 95% and 100% are metrics that assess the part of the ROC curve where the clinical decisions are actually made. Diagnostic likelihood ratios (DLR) can be calculated from sensitivity and specificity based on POM scores and can be useful in comparing technologies in breast imaging.

The Reader-02 Study demonstrated that the Imagio Breast Imaging System supports the proposed indications for use statement as a diagnostic breast imaging device by meeting the primary endpoint.

Specificity at a fixed sensitivity of 98% (fSp)

Specificity at a fixed sensitivity of 98% was analyzed using MRMC analysis (OR-DBM MRMC 2.51, https://perception.lab.uiowa.edu/). Mean (average over all readers) fSp was found to be higher with statistical significance (two-sided p=0.027) for IUS+OA (47.2%, 95% CI=[35.9%,58.5%]) compared to IUS alone (38.2%, 95% CI= [24.9%, 51.6%]), with a difference in fSp of 9.0% with 95% CI=[1.0%, 17.0%]. Thus, IUS+OA achieved the primary endpoint in the Reader-02 Pivotal Study. When the empirical ROC curve is used, interpolation is typically required to estimate fSp because 98% sensitivity may not fall onto the intrinsic grid for the empirical ROC curve. The results above were obtained using endpoint interpolation, which uses the specificities corresponding to the two sensitivities on the intrinsic grid that are closest to 98%. This is the default technique for the MRMC code used in the statistical analysis in this study. Midpoint interpolation, which has a slightly different formulation when a point used for interpolating the fSp lies on a horizontal line segment, provided similar results.

Diagnostic Likelihood Ratios

The observed mean NLR was 0.047 (95% CI: 0.032, 0.062) for IUS+OA suggesting that averaging over all 15 readers in the study a negative test read (POM ≤2%) was observed about 21 (i.e., 1/0.047) times more often among non-cancer cases, compared to those with cancer, and the observed mean NLR was 0.053 (95% CI: 0.037, 0.070) for IUS alone suggesting that averaging over all 15 readers in the study a negative read (POM≤2%) was observed about 19 (i.e., 1/0.053) times more often among non-cancer cases, compared to those with cancer. The decrease (i.e., improvement with IUS+OA compared to IUS alone) in NLR could not be established with statistical significance because the observed relative NLR (the ratio in NLR for IUS+OA and IUS) was 0.896 with a 95% CI= (0.693, 1.11) which included 1 indicating that no evidence of a difference in NLR was found. The confidence intervals above for NLR and the relative NLR do not take into consideration the variability in the reader population and are therefore applicable only to the set of radiologists who took part in the reader study. Since a sequential hierarchical testing to control the study type I error rate was pre-specified, and this was the second hypothesis test in the sequence, and decrease in NLR was not met (i.e., an improvement in NLR for IUS+OA compared to IUS alone could not be shown), not only improvement in NLR for IUS+OA compared to IUS alone cannot be claimed, but hypotheses test results from subsequent hypotheses (for the remaining secondary endpoints of PLR and partial ROC AUC) are not reported. The results reported below for PLR and Partial ROC AUC are considered descriptive or non-confirmatory (and no claims can be made about these).

Based on descriptive statistics that do not control type I error and that cannot be generalized outside this particular study, the observed mean PLR was 1.959 (95%

CI: 1.870, 2.051) for IUS+OA (only as a descriptive result this suggests that averaging over all 15 readers in the study a positive test read (POM>2%) was observed about 2 times more often among cases with cancer, compared to those without cancer), and the mean PLR was reported as 1.548 (95% CI: 1.498, 1.597) for IUS alone (only as a descriptive result this suggests that averaging over all 15 readers in the study a positive test read (POM>2%) was observed about 1.5 times more often among cases with cancer, compared to those without cancer). The descriptive observed relative PLR was 1.281 (95% CI: 1.231, 1.298). The confidence intervals above for PLR and the relative PLR do not take into consideration the variability in the reader population and are therefore applicable only to the set of radiologists who took part in the reader study.

Partial AUC under the ROC curve from 95%-100% sensitivity

pAUC was lower in the hierarchical test order than NLR, which failed to achieve significance. Consequently, pAUC results are not part of the claim structure and are reported as descriptive statistics. The mean unscaled pAUC was 0.0244 (95% CI: 0.0230, 0.0258) for IUS+OA and 0.0205 (95% CI: 0.0191, 0.219) for IUS alone, a difference of 0.0039. All readers had a larger point estimate of pAUC for IUS+OA than for IUS alone.

POM score distributions

The following results are not part of the claim structure and are reported as only descriptive and non-confirmatory results. POM scores were analyzed by computing the mean score among the 15 readers for a given mass with IUS only or with IUS+OA. For IUS+OA, the mean POM for malignant masses was 70.7 (95% CI: 66.86, 73,28) whereas the mean POM for benign masses was 15.90 (95% CI: 13.65, 18.15). For IUS alone, the mean POM for malignant masses was 65.23 (95% CI: 62.38, 68.08) whereas the mean POM for benign masses was 16.41 (95% CI: 14.54, 18.28). The confidence intervals provided above apply only to the average POM score of the 15 readers who participated in the study, and do not generalize to the average POM scores of other readers or the POM scores of individual readers.

Partial AUC and distribution of fSp per years of experience of readers

The following scatter graphs (Figure 5) show the distribution of fSp and pAUC versus number of years of breast imaging experience for benign and for malignant masses.

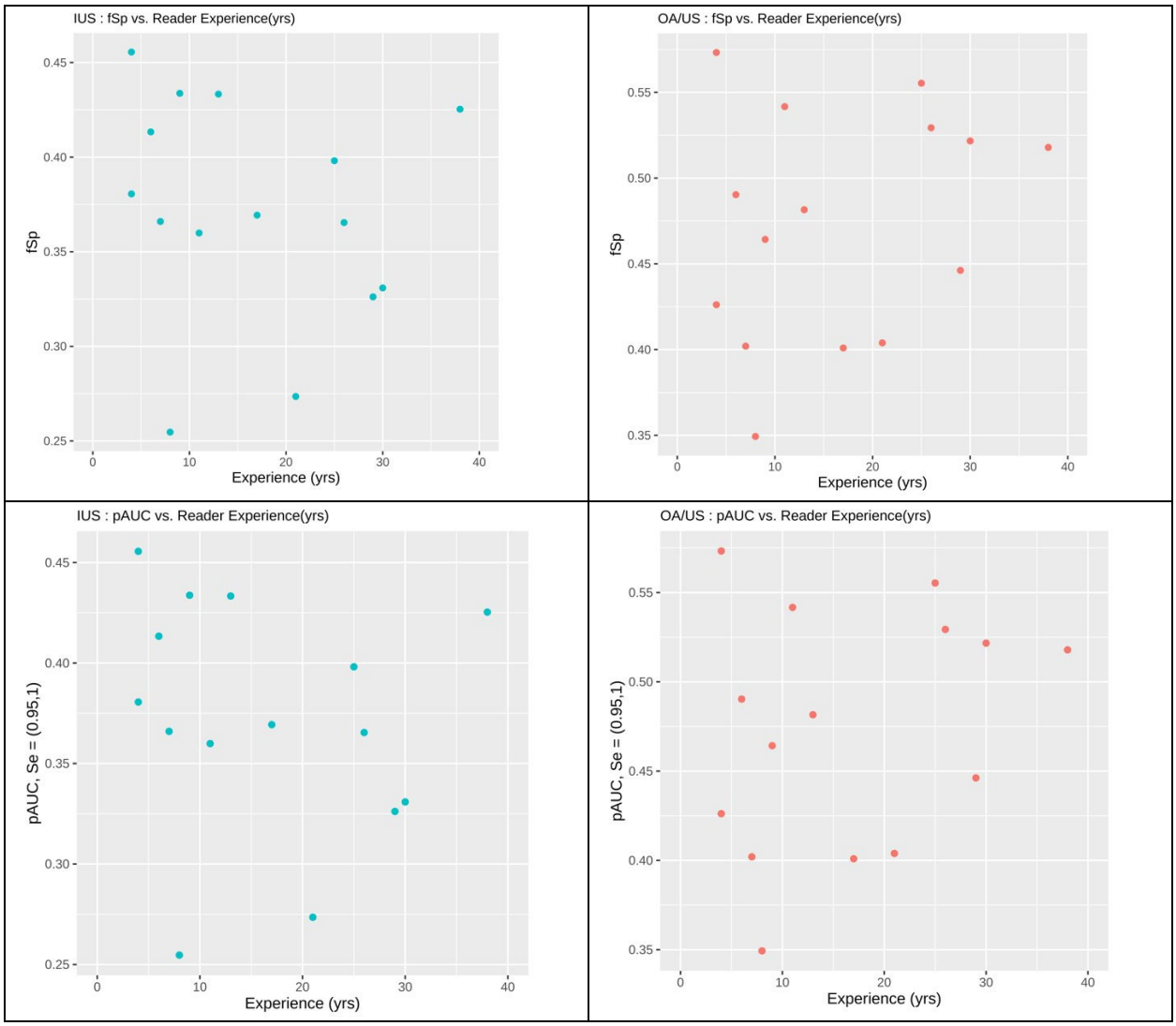

Figure 5: Scatter graph of distribution of fSp (top) and pAUC (bottom) versus years of breast imaging experience for benign (left) and malignant (right) masses

All reader received the same amount of training to prepare for the Reader-02 reads.

The SenoGram

SenoGram classification performance was assessed with descriptive (non-confirmatory) ROC metrics (fSp, pAUC) and classification metrics (sensitivity and specificity) observed on the Reader-02 dataset (and no claims can be made about thses). fSp and pAUC were assessed based on the SenoGram inputs assigned by each reader in Reader02, and then averaged over the 15 readers. Sensitivity and specificity were assessed for each reader at a threshold of 2% for the SenoGram POM output and then averaged. Using endpoint interpolation, the

average fSp was 44.1% (95% CI: 38.4%, 49.8%) and the average pAUC was 0.0232 (95% CI: 0.0215, 0.0249). The average SenoGram sensitivity and specificity were 97.0% (95% CI: 96.0%, 97.9%) and 50.9% (95% CI: 46.0%, 55.8%), respectively.

The binary agreement between readers and SenoGram predictions was measured by comparing results for each case. Reader and SenoGram results agree if both predict positive (cancer) or both predict negative (benign). Readers agreed with the SenoGram results in 98.8% (2667/2700) of cancer cases, 93.3% (4197/4500) of benign+TPB+HR cases, and 95.3% (6864/7200) overall.

3. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. 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 15 independent readers. None of the clinical investigators were full-time or part-time employees of the sponsor and none 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)(3) 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

Nonclinical imaging tests in breast-mimicking tissue phantoms characterized and quantified image quality characteristics of the device. Test results demonstrated the device's ability to detect blood vessel-mimicking targets and measure differences in target blood oxygen saturation. Phantom testing was also used to compare the final device design to the original device design used to collect images in the PIONEER

study. This was necessary as the final device's modified image processing algorithms were used to reprocess clinical images for use in the Reader-02 study.

The Reader-02 Pivotal Study demonstrated that Imagio Breast Imaging System has better specificity than IUS at fixed sensitivity of 98%, and it showed that Imagio Breast Imaging System supports the proposed indications for use as a diagnostic breast imaging device.

B. Safety Conclusions

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

The device is a Class 3B laser product for external exposures (i.e., through the imaging probe) and Class 4 for internal exposures (i.e., during maintenance). Laser exposure is below known safety limits for skin and eye (when wearing appropriate laser safety eyewear). A small number of subjects reported minor AEs including paraesthesia, skin warming, and in one case a second-degree burn that may have actually been contact dermatitis.

C. Benefit-Risk Determination

The probable benefits of the device are determined based on data collected in a clinical study conducted to support PMA approval as described above. The primary benefit of the Imagio Breast Imaging System, using the OA image information, is improved classification of the mass of interest as compared to ultrasound alone in a group of women with BI-RADS 3-5 assessment based on ultrasound imaging. Additional potential benefits of the device include non-ionizing radiation, no significant compression of the breast such as that used in X-ray mammography, and no use of confined spaces such as those used for MRI.

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

The probable risks of the Imagio Breast Imaging System are in terms of diagnostic accuracy, i.e. false positive and false negative. A false positive test would lead to additional imaging evaluation that would be otherwise not be performed. The additional workup would result in increased expense for the patient and risk of additional discomfort and potential complications such as infection resulting from biopsy. The consequence of false negative would be delay in diagnosis, which would happen if the Imagio Breast Imaging System were not used.

Additional factors to be considered in determining probable risks and benefits for the Imagio Breast Imaging System included: 1) physician's complete involvement in the clinical decision making based on full patient history, 2) lack of an alternative product that would visualize the tissue oxygenation which has shown to be of critical

importance in breast cancer, 3) high clinical significance of breast cancer screening and diagnosis at early stages of the disease, minimal adverse events that are primarily due to laser irradiation of the skin, a reversible effect, 4) appropriate training, and comprehensive labeling to allow optimal use of the device.

Patient Perspective:
This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, the performance data support that the probable benefits of using Imagio Breast Imaging System for the proposed indications for use 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. The nonclinical studies demonstrated that the Imagio Breast Imaging System design met required specifications for safety and effectiveness. Phantom studies enabled characterization and quantification of image quality, vessel detectability, and oximetry measurement, thus establishing reasonable expectations and limitations for *in vivo* performance. The clinical study results suggest that the Imagio Breast Imaging System can result in improved classification of the mass of interest in group of women with BI-RADS 3-5 assessment; using the OA image information as compared to ultrasound alone.

XIII. CDRH DECISION

CDRH issued an approval order on 01/11/2021.

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.