SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Ultrasound Imaging Device

Device Trade Name: SoftVue™ Automated Whole Breast Ultrasound System with Sequr™ Breast Interface Assembly

Device Procode: PAA

Applicant's Name and Address: Delphinus Medical Technologies, Inc.
45525 Grand River Avenue
Novi, MI 48374 USA

Date(s) of Panel Recommendation: Not Applicable

Premarket Approval Application (PMA) Number: P200040

Date of FDA Notice of Approval: 10/06/2021

Priority Review: Not Applicable

Breakthrough Device: Not Applicable

II. INDICATIONS FOR USE

The SoftVue system is indicated as an adjunct to mammography for breast cancer screening in asymptomatic women with dense breast parenchyma after confirmation that the breast density composition is BI-RADS c or d at the time of screening mammography. The device is intended to increase breast cancer detection in the described patient population relative to mammography alone. The device is not intended to be used as a replacement for screening mammography. The device can be used at the same visit as screening mammography and SoftVue images are intended to be interpreted with the mammogram results to enhance screening.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

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

V.   DEVICE DESCRIPTION

The SoftVue™ Automated Whole Breast Ultrasound System with Sequr™ Breast Interface Assembly (referred in this document as the SoftVue System) is an ultrasound imaging device that is specifically designed for the breast. The patient lies prone on a bed that is equipped with a water-tank to accommodate a pendulous breast to be submerged in a warm water bath up to the chest wall. A ring of transducers that is permanently installed in the water tank will be used to acquire ultrasound signals from the breast, via coupling through water. The device operates in an automated fashion to collect three-dimensional (3D), whole breast tomographic ultrasound imaging, by moving the ring of transducers vertically for acquiring ultrasound image slices of the breast. A photograph of the device is shown below, in **Figure 1**.

Figure 1: Photograph of SoftVue System

As noted above, a ring of transducers that is permanently installed in the water tank will be used to acquire ultrasound signals from the breast. The transducers have a central frequency of 3 MHz, with all acquisition parameters, including the acoustic output, pulse repetition frequency, pulse duration, and depth, that are preset, and cannot be changed by the operator." A schematic diagram of the ring of transducers is shown below, in **Figure 2**.
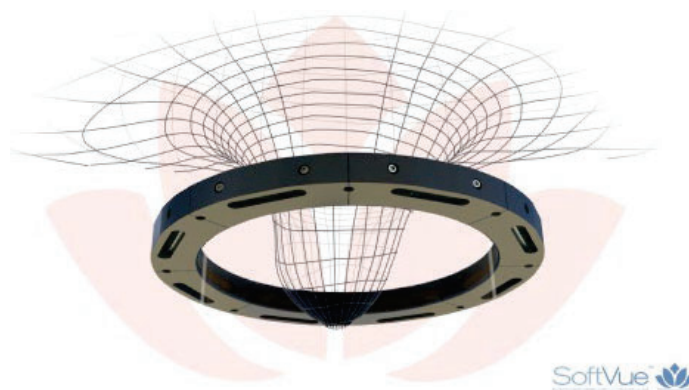

Figure 2: Schematic Diagram of the Ring of Transducers

The subject device includes a flexible patient interface membrane with a central aperture that is placed on top of the water tank. This membrane allows the breast being positioned in the water bath, and keeping the water from overflowing from the tank. A photograph and a schematic diagram of the membrane are shown below, in **Figure 3**.
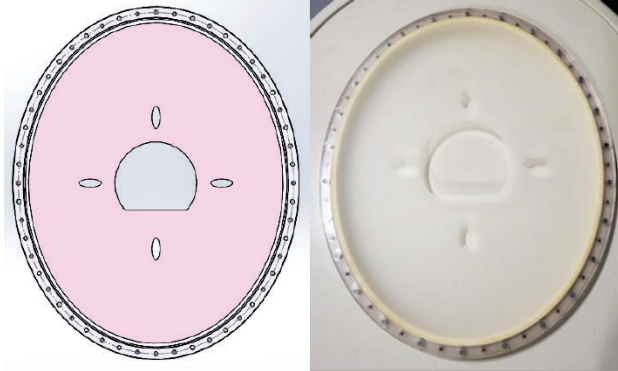

Figure 3: A Photograph (Right) and a Schematic Diagram of the Membrane (Left)

The SoftVue System includes a water conditioning system that filters, degasses, and heats the inlet water, pumps the water into and out of the imaging chamber, and drains spillage from the imaging chamber and reservoir.

The SoftVue System includes a Breast Interface Assembly (BIA), anchored to the bottom of the water tank, that is used to center, shape, and stabilize the breast for optimal imaging in the water bath. Photographs of the BIA are shown below, in **Figure 4**.

Figure 4: Photographs of the BIA

The breast is anchored to the Sequr Breast Interface (SBI), via suction on the nipple, facilitating pulling the breast downward to elongate it. The breast elongation is done to facilitate imaging of the entire breast by optimizing the number of image slices acquired during the scanning procedure.

The SoftVue System collects the following types of information: ultrasound reflection, sound speed, and attenuation, all in coronal planes of the breast. The information from these three signal sources are used to reconstruct, and make available to the users, five types of images: reflection, sound speed, attenuation, wafer (reflection image enhanced by sound speed information), and relative stiffness (sound speed enhanced by attenuation information), as shown below, in **Figure 5**:
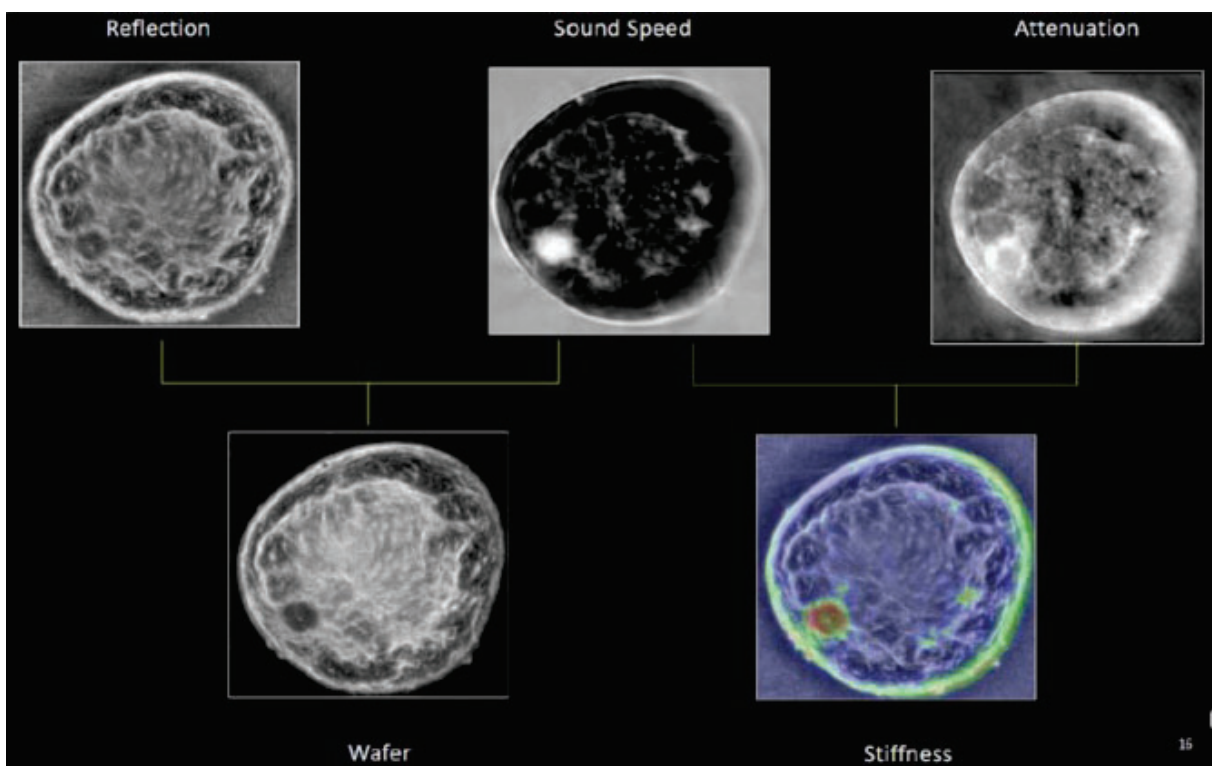

Figure 5: The Various Images of the SoftVue System

The SoftVue system acquires coronal images for the volume of the breast, from the nipple to the chest wall, in parallel slices. It is important to note that the breast volume coverage is dependent on how much of the breast is submerged in the water.

The final Brightness-mode (B-mode) images are based on reconstructive algorithms that utilize signals that have propagated through the patient's breast, i.e. transmitted by one transducer and received by other transducers in the ring. Both through transmission amplitude, and speed of sound information are used for image reconstruction.

The accuracy for each of the image types is provided below. The values specified in **Table 1**, below, are considered measurement accuracies of various image types.

Table 1: The Image Dimensional Accuracy of the Various Images of the SoftVue System

Image Modality	Distance Accuracy	Value Accuracy	Spatial Resolution	Contrast to Noise Ratio
Attenuation	< 15% for 1 cm; < 5% for 15 cm	± 0.8 dB/cm/MHz; 0-10 dB/cm/MHz	< 6.0 mm	N/A
Reflection	< 15% for 4 mm; < 5% for 15 cm	N/A	< 1.5 mm	> 1.5
Sound speed	< 15% for 1 cm; < 5% for 15 cm	± 10 m/s; 1400-1600 m/s	< 15.0 mm	N/A
Relative Stiffness	< 15% for 1 cm; < 5% for 15 cm	N/A	< 3.0 mm	N/A
Wafer	< 15% for 4 mm; < 5% for 15 cm	N/A	< 1.0 mm	> 1.5

The user interacts with the SoftVue System via a touchscreen display monitor and quick response (QR) code scanner. The touchscreen display monitor allows the user to enter patient information, navigate through the operation of the SoftVue System, and adjust system settings such as the time and date format, user information, and network settings for the external Picture Archiving and Communication System (PACS). The monitor displays patient information, system status information and live video camera feeds of the imaging chamber that are used to assist in positioning the breast. The QR code scanner is used to scan a new SBI into the system for each imaging procedure to ensure that SBI units are not reused for multiple patients.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

X-ray mammography (XRM) is the primary imaging modality that is marketed and labeled for breast cancer screening. However, increased breast tissue density is the most significant factor limiting the effectiveness of mammographic screening, and approximately 40% of women who participate in organized mammography screening have dense breast tissue [1, 2]. The sensitivity of mammography is reduced by 36% to 38% for women with dense breast tissue in comparison to the sensitivity of mammography for women with non-dense breast tissue, because dense breast tissue can conceal malignant lesions [1, 3].

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

A similar class III product that is commercially available is the Invenia ABUS system. Currently, this is the only other device offering automated breast ultrasound, as an adjunct to mammography for breast cancer screening in asymptomatic women.

VII. MARKETING HISTORY

The SoftVue System has class II clearance (the most recent being via K172256), for the following indications for use: "SoftVue™ is indicated for use as a B-mode ultrasonic imaging system for imaging of a patient's breast when used with an automatic scanning curvilinear array transducer. The device is not intended to be used as a replacement for screening mammography."

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The Prospective Case Collection Registry reported a small number of non-serious, non-severe adverse events (13 in Arm 1 for a rate of 0.2%). The events were primarily related to patient discomfort related to position on the exam table.

All of the reported events were associated with slight discomfort during the exam, in many cases related to table position rather than the SoftVue system itself. The very low level of events (0.2%) supports the safety of this product.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The non-clinical laboratory testing have been performed for the various components of the subject device. The SoftVue System includes the following components, shown below, in **Figure 6**.
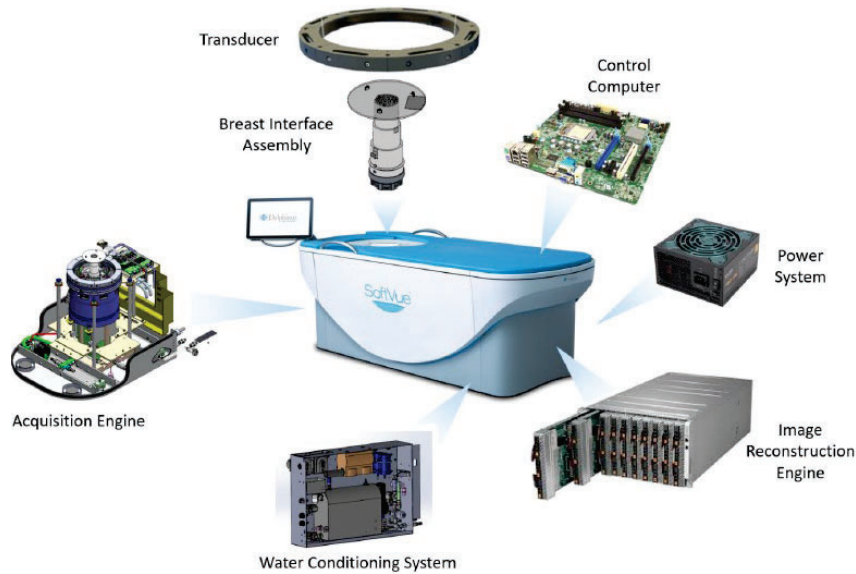
Figure 6: The SoftVue System and its Components

The SoftVue System, intended for premarket approval and commercialization, is based on the 510(k)-cleared SoftVue 3.0 design (K172256) as used for the Prospective Case Collection (PCC) registry. The SoftVue System's operating principles and physical and operational specifications are equivalent to the 510(k)-cleared SoftVue 3.0 device. However, improvements for commercial use were incorporated. These improvements were documented in accordance with applicable Quality System regulations and Delphinus Medical Technologies (DMT) documentation procedures.

A design verification and validation plan was created to identify all activities necessary, resources needed, and the strategy to verify and validate the SoftVue System in order to demonstrate that the SoftVue System design meets its design input requirements, user needs, and intended use. Each plan outlines the nonclinical planned activities and deliverables related to verification and validation of the SoftVue System, including the overall system, subsystems, and associated documentation.

Design Verification and Validation
These activities were as follows:

1. Subsystem design verification
   The SoftVue System has undergone subsystem design verification testing to verify the physical, functional, and performance characteristics of its Transducer, Table/Housing, Water Conditioning System, Computer Control System, Power System, Data Acquisition System and Sequr Breast Interface. Test methods were defined in associated protocols, covering all design requirements.

   Testing demonstrated that the design outputs for the subsystems met the design inputs. The failed tests were noted as issues that were analyzed appropriately.

2. System level verification
The SoftVue System has undergone system design verification testing to verify the physical, functional, and performance characteristics of the interfaces between subsystems and the system as a whole. System verification testing included verification of the effectiveness of risk controls. Test methods were defined in associated protocols. The Sequr Breast Interface (SBI) accessory has also undergone design verification testing to verify the physical and functional requirements of the SoftVue System's consumable. Verification testing also included confirmation of the SBI's packaging requirements. The failed tests are noted as issues that are analyzed appropriately.

Also, it is noted that some changes were made after the initial testing. In such cases, med an analysis was performed to determine the possible affected requirements, retesting the affected requirements.

The SoftVue System and Sequr Breast Interface accessory met their respective design input requirements.

3. Validation testing (usability)
The SoftVue System has undergone validation testing including usability and human factors evaluation. Validation consisted of simulated users and simulated patients using the SoftVue System, as well as simulated technicians servicing the SoftVue System. Testing was conducted at Delphinus' Novi, MI location in a room set up to simulate a professional clinical setting on a production equivalent SoftVue System. Standard, production-level Sequr Breast Interfaces were also used. The validation included test cases to exercise the workflow along with a survey interview with the simulated users.

The SoftVue System and Sequr Breast Interface met their respective user requirements.

Also, the sponsor has noted that during the course of the clinical studies "more than 8000 patients were exposed to the product and more than 70 radiologists were trained and performed SoftVue image review. Also, more than 20 technologists and more than a dozen study coordinators performed imaging procedures using SoftVue." The patient feedback provided further information on the subject device's usability. The sponsor has concluded that "the responses in > 90-95% of subjects were always positive confirming the acceptance of the technology.

4. Biocompatibility
The biocompatibility of the SoftVue patient-contacting materials, including the Sequr Breast Interface (SBI), was tested pursuant to ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process, which specifically outlines the types of biocompatibility tests that are required based on the nature of the device and the extent and

duration of its contact with blood or tissues. All direct and indirect contacting materials were identified and analyzed for a safe history of use in SoftVue. Based on the analysis and testing, it was concluded that when used as intended, the materials with direct or indirect skin contact in SoftVue are biocompatible with human operators and users.

5. Electrical Safety and Electromagnetic Compatibility

As a medical electrical device, SoftVue is compliant with IEC 60601 and its collateral and particular standards. **Tables 2** and **3**, below provide the summary of the electrical safety, and electromagnetic compatibility (EMC), respectively:

Table 2: Summary of IEC 60601 Compliance Testing

Standard Organization	Reference # and Date	Standard Title
IEC	60601-1:2005 + Corr. 1:2006 + Corr. 2:2007 + A1:2012	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
IEC	60601-1-2:2014	Class A for Conducted Emissions, Immunity for Professional Healthcare Facility Environment
IEC	60601-1-6:2010, AMDI:2013 for use in conjunction with IEC 60601-1:2005 + Corr. 1:2006 + Corr. 2:2007	Medical electrical equipment - Part 1-6: General requirements for safety - Collateral Standard: Usability
IEC	60601-2-37, am1 for use in conjunction with IEC60601-1, am1 with Corr1 and Corr2	Medical electrical equipment - Part 2: Particular requirements for the safety of ultrasonic medical diagnostic and monitoring equipment
IEC	60825-1 Edition 2.0 2007-03	Safety of laser products - Part 1: Equipment classification, and requirements [Including: Technical Corrigendum 1 (2008), Interpretation Sheet 1 (2007), Interpretation Sheet 2 (2007)]
IEC	62304:2006 + A1:2015	Medical device software - Software life-cycle processes
ISO	14971:2007	Medical devices – Application of risk management to medical devices

Table 3: Summary of EMC Testing

Test Standard / Test Method	Test	Result
IEC 60601-1-2 / CISPR 11:2009/AMD1:2010	Conducted Emissions	Pass
IEC 60601-1-2 / CISPR 11:2009/AMD1:2010	Radiated Emissions	Pass
IEC 60601-1-2 / IEC 61000-3:2005/AMD2:2009	Harmonic Current Emissions	N/A
IEC 60601-1-2 / IEC 61000-3-3:2013	Voltage Fluctuations Emissions	N/A
IEC 60601-1-2 / IEC 61000-4-2:2008	Electrostatic Discharge Immunity	Pass
IEC 60601-1-2 / IEC 61000-4-3:2006/AMD2:2010	Radiated RF Electromagnetic Fields Immunity	Pass
IEC 60601-1-2, 8.10 / IEC 61000-4-3:2006/AMD2:2010	Immunity to proximity fields from RF wireless communications equipment	Pass
IEC 60601-1-2 / IEC 61000-4-4:2012	Electrical Fast Transients and Bursts Immunity	Pass
IEC 60601-1-2 / IEC 61000-4-5:2005	Surges Immunity	Pass
IEC 60601-1-2 / IEC 61000-4-6:2013	Conducted Disturbances, Induced by RF Fields Immunity	Pass
IEC 60601-1-2 / IEC 61000-4-8:2009	Power Frequency Magnetic Fields Immunity	Pass
IEC 60601-1-2 / IEC 61000-4-11:2004	Voltage Dips Immunity	N/A
IEC 60601-1-2 / IEC 61000-4-11:2004	Voltage Interruptions Immunity	Pass

The reports show passing results where applicable. The device labeling includes appropriate information regarding the EMC.

6. Storage and Tranportation Testing

   Storage and transportation testing were performed on the SoftVue System. All required storage and transportation testing were conducted per associated standards listed in **Table 4**, below:

Table 4: Shipping Standards

Standard Organization	Reference # and Date	Standard Title	Product	Result
ISTA	3A:2018	Packaged-Products for Parcel Delivery System Shipment 70 kg (150 lb.) or Less	Sequr	PASS
ISTA	3B:2017	Packaged-Products for Less-Than-Truckload (LTL) Shipment	SoftVue	PASS

The purpose of this testing was to establish the ability of the shipping container to adequately protect the Device, after exposure to environmental hazards associated with operational and transportation conditions. A calibration and imaging

procedure were performed with the SoftVue prior to any environmental conditioning to confirm the system was functional prior to testing.

The SoftVue System passed all shipping and transportation testing as well as environmental testing.

7. Software
    The SoftVue System software is released as two components for practicality – the "SoftVue Software" and the "SoftVue Core Software." The SoftVue Core Software consists of operating systems, their configurations, and one software item – the Installation Console Application. The Installation Console Application is used to install SoftVue Software on top of the operating systems. All SoftVue software verification and validation activities were performed on a compatible pair of SoftVue Core Software and SoftVue Software. The specific versions of each are defined in the software verification plans and reports.

    The software components of the SoftVue System present a Moderate Level of Concern as defined in FDA's Guidance Document entitled, "*Guidance for the Content of Premarket Submission for Software Contained in Medical Devices,*" issued May 11, 2005. As such, the PMA includes all software documentation required for a Moderate Level of Concern device.

    Based on the Software Requirements Specifications (SRS), software test plans were developed to verify that the respective software meets the defined requirements. Software Verification Test Cases were used to document the test methods for verification of the design outputs. Each element of the SRS was tested and determined to pass all of the specified requirements.

    The SoftVue System incorporates off-the-shelf (OTS) software components, referred to as Software of Unknown Provenance in the Software Lifecycle Process and associated outputs. Accordingly, OTS software documentation for the SoftVue System was performed in accordance with the FDA Guidance Document entitled, "Off-The-Shelf Software Use in Medical Devices," issued September 27, 2019. The validation, risk management and configuration control of the OTS software is documented through the system level documents. The analysis supports the acceptable use of the OTS software components within the SoftVue System per the guidance.

    Lastly, a cybersecurity assessment of the SoftVue System was performed in accordance with the FDA Guidance Document entitled, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices," issued October 2, 2014. Per the cybersecurity assessment, potential hazards, and mitigation strategies were analyzed for the SoftVue System. All identified hazards have been mitigated as far as reasonably possible.

B. **Animal Studies**

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

C. **Additional Studies**

None

X. **SUMMARY OF PRIMARY CLINICAL STUDY(IES)**

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of scanning the breasts with the SoftVue System for breast cancer screening in the United States . Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. **Study Design**

The Clinical data accumulated in support of Premarket Approval (PMA) for the SoftVue System includes a series of Multi-Reader Multi-Case (MRMC) Retrospective Reader Studies (RRS), conducted by Delphinus. A separate initiative, a Prospective Case Collection (PCC) registry, was designed to collect subject images and demographic data from multiple clinical centers where SoftVue was performed at the same visit as routine screening mammography. This registry provided the repository of data that was used for case selection to conduct the RRS. Currently, the PCC registry is closed to enrollment and the only remaining activity is follow-up assessments.

The RRS includes one pilot (RRS1) and two pivotal studies (RRS2 and RRS3). The pilot MRMC retrospective reader study provided critical insight into the training programs for readers and enabled refinement of the SoftVue curriculum, as necessary. The initial aim was for the RRS2 to serve as the pivotal study however, a technical finding required certain cases to be excluded from analysis. Specifically, based on disparity noted in the results of RRS2 in comparison with RRS1, a root cause analysis identified a system software configuration change affecting the available range of the SoftVue breast extension suction.   The suction level range was expanded to allow for lower suction levels to be selected by technologists. The modification, implemented based upon feedback noting patient discomfort and pulsing of the breast extension suction component, unexpectedly resulted in a reduced breast extension across all cases to a level where it was not being operated as intended. As a result, the cases with SoftVue images acquired after the date of this system modification were excluded and a final pivotal reader study, RRS3 was conducted and a supportive analysis of the intended image cohort was performed with the RRS2 data set.

The original suction level range was therefore reinstated and this range was implemented for the commercial product to match the range used for cases in RRS3. Further, at the time the final pivotal RRS3 was conducted, there were a number of cases that had "aged out" of satisfying the eligibility criteria to complete the next annual mammogram within 456 days, so they were also determined to be ineligible for analysis and excluded from RRS3. One additional case was also required to be removed due to the fact that it was discovered during routine clinical site monitoring of the PCC registry that the subject had an eligibility criteria deviation (exclusion for nipple discharge). This resulted in a final cohort of 140 cases for the RRS3 eligible analysis.

A summary of the study design for each trial is provided **Table 5**.

Table 5: Summary of Reader Study Designs

Study Characteristics	RRS1	RRS2	RRS3
Title	A retrospective, observational, case-controlled, multi-reader, multi-case, receiver operating characteristic (ROC) study of reader performance when SoftVue automated breast ultrasound (SV) and digital screening mammography (FFDM) are combined, compared to screening mammography alone, in asymptomatic women with heterogeneous or extremely dense breast parenchyma.	A retrospective, observational, case-controlled, multi-reader, multi-case, receiver operating characteristic (ROC) study of reader performance when SoftVue automated breast ultrasound (SV) and digital screening mammography (FFDM) are combined, compared to screening mammography alone, in asymptomatic women with heterogeneous or extremely dense breast parenchyma.	A retrospective, observational, case-controlled, multi-reader, multi-case, receiver operating characteristic (ROC) study of reader performance when SoftVue automated breast ultrasound (SV) and digital screening mammography (FFDM) are combined, compared to screening mammography alone, in asymptomatic women with heterogeneous or extremely dense breast parenchyma.
Study Design	Multi-reader multi-case (MRMC) ROC study design		
Number of Readers/Cases	A sample size of 100 cases, 20 cancers and 80 non-cancers, were analyzed with 6 unique readers.	A sample size of 200 cases, 50 cancers and 150 non-cancers, were analyzed with 32 unique readers.	A sample size of 140 cases, 36 cancers and 104 non-cancers, were analyzed with 32 unique readers.

Study Characteristics	RRS1	RRS2	RRS3
Objective	The objective of the retrospective reader study is to evaluate the safety and effectiveness of combining SoftVue (SV) automated whole breast ultrasound with screening digital mammography (FFDM) in accurately detecting breast cancer. As part of this evaluation we will obtain information that can be used to properly plan, design, and power future reader studies.	The primary objective of this study is to determine whether the area under the receiver operating characteristic (ROC) curve (AUC) for conventional screening digital mammography (FFDM) plus SoftVue automated whole breast ultrasound (SV; FFDM + SV), averaged across readers, is superior to the AUC for FFDM alone, where calculation of AUC will require correct breast laterality localization.	
Primary Endpoint	The primary endpoint on this study is area under the ROC curve (AUC) requiring correct lesion localization. The primary endpoint is measured on the FFDM read and FFDM+SV read, and compared between them.	The primary endpoint on this study is area under the ROC curve (AUC), requiring correct breast laterality localization. AUCs for each reader estimated in each review condition (FFDM, FFDM+SV), based on the reader assigned per-case malignancy scores with correct breast laterality localization.	The primary endpoint on this study is area under the ROC curve (AUC) requiring correct breast laterality localization.
Secondary Endpoints	Secondary endpoints are sensitivity requiring correct lesion localization, and specificity. The secondary endpoints	The secondary endpoints are to demonstrate an improvement in sensitivity, where correct breast	The secondary endpoints are to demonstrate an improvement in sensitivity, where correct breast

Study Characteristics	RRS1	RRS2	RRS3
	are measured on the FFDM read and FFDM+SV read, and compared between them.	laterality localization is required, and non-inferiority of specificity within a 10% margin, where scores of BI-RADS 4a or higher are considered positive test results.	laterality localization is required, and non-inferiority of specificity within a 10% margin.
Supportive/Sensitivity Analyses	None	Supportive analysis based on per-case AUC requiring correct lesion localization, where the true location is determined as described truthing methodology.	Sensitivity and specificity analyses were conducted based on per-case AUC requiring correct lesion localization, where the true location is determined as described truthing methodology. Sensitivity is tested for superiority and specificity is aimed at demonstrating non-inferiority within a 10% margin.

Figure 7 , below, the Study Consort Diagram, provides a summary of the catalog of images that were amenable to be used for pivotal study analysis.
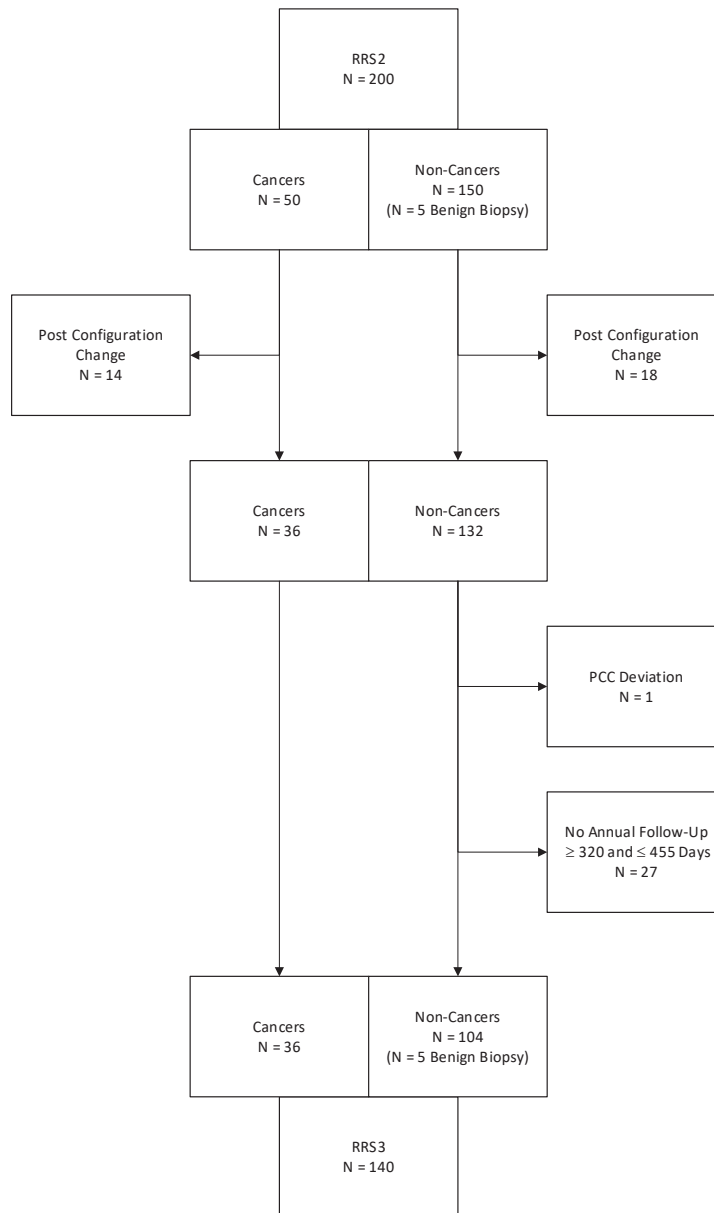
Figure 7: Study Consort Diagram

The three clinical studies, RRS1, RRS2 and RRS3, were conducted between September 2018 and March 2020. The RRS1 study was a formative study or pilot trial that provided the basis to design and power the pivotal studies; it also provided initial feedback during the early development of the SoftVue user training curriculum. RRS2 was originally designed as a pivotal trial with 200 cases and 32 readers, but upon identifying 60 inappropriate cases as described above, the study was repeated as RRS3 with a set of 32 new readers and the 140 cases which met criteria for inclusion.

A protocol compliant analysis for RRS2 was performed and formed the basis of the RRS3 protocol. The analysis was done by removing subjects from the original RRS2 cohort of 200 subjects and analyzing the balance of cases (n = 140; 36 Cancers/104 Non-

Cancers) in a per protocol-compliant analysis. This per protocol analysis of RRS2 is further support for the conclusions of RRS3.

There were three different reasons for the images being excluded:
        1) a software configuration change affecting breast extension suction,
        2) no available one-year follow up completed by ≤455 days and
        3) a PCC registry eligibility criteria deviation.

A summary of cases excluded with the associated reason are summarized in **Table 6**, below.

Table 6: Excluded Images from Retrospective Reader Study 3 (RRS3) Analysis: Reason and Case Type (n=60)

Case Type	Configuration Change (SV imaging on or after 5 September 2018)	No one-year follow-up was completed by ≤455 days	PCC registry eligibility deviation
Cancer	14	0	0
Non-Cancer	18	27	1

The Truthing procedure was performed to verify the gold standard location of each cancer lesion to establish the basis of comparison for the ROC analysis. This "ground truth" was utilized for evaluation of all cancers based upon confirmed pathology/surgical reports and not on any screening imaging, mammography or SoftVue. All confirmed cancers were subjected to the exact same truthing procedure.

An independent radiologist, utilizing all relevant case data provided by the enrolling center (medical records, diagnostic imaging and pathology/surgical reports), indicated electronically the location of the site that was biopsied with subsequent confirmed malignant pathology outcome. The independent radiologist was a Board-Certified Radiologist that is also Mammography Quality Standards Act (MQSA) qualified individual that had demonstrated experience and expertise to conduct this process.

Based upon interactions with FDA, a revised truthing process was performed on 20-22 April 2021 to reduce any potential bias. The revised truthing process included three independent radiologists, as opposed to a single truther, that were masked to the content of SoftVue images.

The final size of the tumor was obtained from the final pathology report resulting from the excision of the tumor mass and any subsequent excisions of positive margins, as appropriate. The electronic marker placement locations from the images, together with the size measurements and the final pathology results were used to electronically define the truth target area (FFDM) or target volume (SV) within the digital mammography and

SoftVue images for each cancer case, against which the Reader's markers compared for analysis.

The distance from ground truth to the reader markers established during the RRS studies was tailored for comparison of the 2D Mammogram image against the 3D SoftVue images. The three truther positions were combined, and a single analysis of the reader study results against the combined position was performed. The truther positions were combined as follows:

- For mammo (2D), each of the three truther positions defined the center of a disk whose diameter was set to the maximum between 30 mm and the lesion size. The matching region was then specified as the convex hull defined by these three disks, as illustrated in **Figure 8**. A match occurred when the reader marking was located within that convex hull, in either the cradiocaudal (CC) or mediolateral obique (MLO) views.

- For SoftVue, the same strategy was applied in 3D, with the three truther positions defining the center of spheres, and the matching region defined as the convex hull of these three spheres.

If a reader marker was within the convex hull it was counted as a lesion localization, whereas if it were outside of the convex hull, it was considered a non-localization. The reader was considered to have identified a cancer case if she or he localized at least one malignant lesion, and to have missed the case if no reader marker was within the convex hull of any malignant lesion in the case.
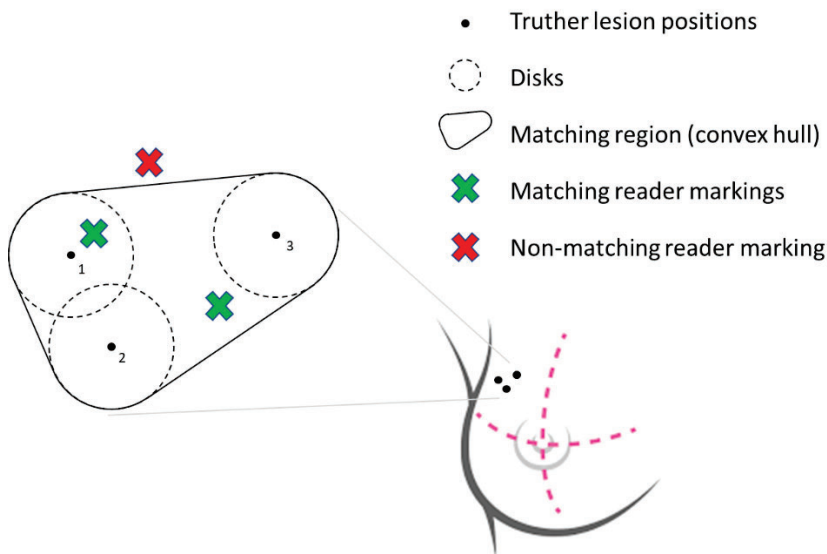

Figure 8: Two-dimensional matching region defined as the convex hull of the three disks whose centers are set to the truther lesion positions.

The reader assigned a BI-RAD Category for the case and a malignancy score of (0-100) for every marked lesion, as well as a malignancy score for the overall case (**Table 7**). These scores were used to characterize the tumors.

Table 7: Malignancy Scoring

Impression	Malignancy Score
Negative/Benign	0-20
Likely Benign	21-40
Possibly Malignant	41-60
Probably Malignant	61-80
Definitely Malignant	81-100

1. Clinical Inclusion and Exclusion Criteria
    The cases used for the RRS Studies were obtained from the ongoing Prospective Case Clinical (PCC) Registry. This registry enrolled subjects between July 2017 and April 2019. As indicated previously, images collected with the unintended software configuration were not eligible for RRS3. The eligible cases were enrolled between October 2017, and September 2018, prior to the configuration change. The registry has completed enrollment, however, follow up is still ongoing with participants pending return to the imaging centers for their next annual mammogram. The PCC registry program has several aims including establishing a library of images to be used for the reader studies, to support research and development efforts, to supply images for marketing materials and/or to supply cases and gather information for training curriculum development (highlighted as different study "arms"). Images were acquired from asymptomatic women at their normally scheduled yearly breast imaging exam for use in the RRS Studies.

    The eligibility criteria for this specific arm (Arm 1) of the PCC include the following:

    - Female genotype XX or XXX by patient self-report
    - Any race or ethnicity by patient self-report
    - Age 18 or older
    - Provides informed consent and completes participant questionnaire
    - Willing to comply with protocol and follow-up recommendations as described in consent form
    - Asymptomatic by self-report (non-suspicious symptoms, as determined by standard practices, such as no findings of concern on clinical breast exam are eligible for enrollment when diagnostic imaging is not indicated)
    - Complete screening FFDM and digital breast tomosynthesis (DBT) views captured (bilateral CC and MLO)

- BI-RADS density composition category c or d on preliminary assessment of FFDM
- Agrees to complete the next annual screening exam in 12 months
- Agrees to undergo all standard of care additional imaging and diagnostic procedures
- Agrees to report any breast changes or symptoms until completion of the next annual exam
- Agrees to be contacted by site staff if next annual exam or recommended diagnostic exams are not completed within the appropriate timeframe

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

- Weight exceeds 350 lbs. by self-report
- Less than 7 days have transpired since breast biopsy or has persistent hematoma from breast biopsy
- Currently pregnant or lactating by patient self-report
- Nipple discharge, weeping rash, open wounds, or unhealed sores on the breast
- Bilateral mastectomy
- Unable to lay prone on the scan table for up to 15 minutes
- Unable to provide written Informed Consent and complete the Participant Questionnaire
- History of breast cancer diagnosis and/or treatment (chemotherapy, surgery, and/or radiation) in the past 12 months per medical record or patient self-report
- Unwilling/unable to comply with the protocol, annual follow-up, or diagnostic recommendations

The cases for the pivotal, Retrospective Reader Study (RRS2/3) included 200 breast screening cases with 50 confirmed cancers from the PCC in RRS2. From this cohort, the RRS3 study ultimately utilized 140 cases. The group includes 36 confirmed cancers and 104 non-cancers. Both the RRS2 and the RRS3 Studies were performed with separate groups of 32 radiologists that were American Board of Radiology Certified and MQSA Qualified. Based upon the fact that there was a requirement to remove images from the analysis of RRS2 data (identified as images acquired prior to September 4, 2018), the study was repeated with new readers in RRS3 with the final data set of 140 cases.

RRS3 utilized the intended commercial training curriculum which was refined based upon the learnings from RRS1 and RRS2. As indicated previously, the SoftVue images that were identified during RRS2 data analysis to be operating in an unintended range due to a breast extension software modification made to maximize patient comfort, were removed for the RRS3 study. As indicated previously, one image from the selected cohort was also identified to deviate from the eligibility criteria and was therefore removed (subsequent identification of a subject that had

nipple discharge after subject enrollment. **Figure 7** provides a consort diagram depicting the image selection process between RRS2 and RRS3.

The inclusion criteria for the RRS2 and RRS3 pivotal studies were as follows:
- Consented, eligible female subjects with dense breasts (BI-RADS c or d) enrolled in Phase B of Arm 1 of Delphinus' Prospective Case Collection (PCC) Protocol #DMT-2015.001 with SoftVue acquisition before 5 September 2018.
- Either:
  - Cancer: Malignant pathology results after breast biopsy on lesions detected by any screening or diagnostic modality between enrollment imaging and ≤455 days from enrollment imaging; or
  - Non-Cancer: Normal or negative screening and/or benign or probably benign diagnostic imaging at enrollment and Non-Cancer status confirmed by negative or benign annual follow-up performed after one year (320 to 455 days), or benign breast biopsy pathology confirmed within 455 days from enrollment imaging, with no malignant breast pathology diagnosed.
- Source records available for verification including verification of case reference standard (cancer, benign, non-cancer).
- Completed FFDM (CC and MLO views for both breasts) and SV (one volume per breast) imaging per PCC (Protocol #DMT-2015.001 Arm 1).
- Bilateral FFDM images and SV images available as digital image files able to be displayed on workstation review software for quality control review, with sufficient anatomical coverage and exam quality as determined by the enrolling PCC radiologist. Only conventional FFDM images will be utilized, no synthetic images from DBT are allowed.

The exclusion criteria for the RRS2 and RRS3 pivotal studies were as follows:
- Subjects who are not Phase B or had SV performed on or after 5 September 2018
- Subjects who are not eligible for or are in violation of PCC Protocol #DMT-2015.001 Arm 1.
- Subjects who previously enrolled in PCC Protocol #DMT-2015.001 Arm 2, and then subsequently enrolled in Arm 1.
- Subjects for whom >455 days have passed since enrollment imaging on Protocol #DMT-2015.001 Arm 1, but for whom no biopsy nor no one-year follow-up was completed by ≤455 days.
- Subjects without complete data and source records available for ground truth verification and GCP/ICH auditing
- Subjects with Protocol #DMT-2015.001 Arm 1 (FFDM and SV) imaging that is incomplete; or complete but not available as digital image files able to be displayed on workstation review software for quality control review; or complete and determined through quality control review to have insufficient anatomical coverage and/or exam quality.

- Subjects who were Withdrawn or Lost to Follow-Up from Protocol #DMT-2015.001 Arm 1 due to a major protocol deviation, non-compliance with standard of care recommendations, or voluntary request to revoke consent.

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at one year, to be completed by ≤ 455 after being scanned by the SoftVue system.

3. Clinical Endpoints

   As outlined above, the primary endpoint for RRS2 and RRS3 are consistent; the area under the ROC curve (AUC) requiring correct breast laterality localization. A secondary set of endpoints were aimed at demonstrating superiority in reader sensitivity and non-inferiority in specificity within a 10% margin for FFDM + SV compared to FFDM alone.

   In RRS2, a prespecified supportive analysis of ROC curve (AUC) requiring correct breast localization was also specified. This analysis was carried out for RRS3 as well, since this supportive analysis is most relevant for the intended use of SoftVue. In addition, per protocol analyses were completed for RRS2 as well as RRS3 inclusive of the 140 final images. This combined set of results from RRS2 and RRS3 are supportive of the intended use.

B. Accountability of PMA Cohort

All cases were categorized into the following case types:

Cancer cases, confirmed by breast biopsy with at least one lesion determined to be malignant by pathology:
- Detected at enrollment in Protocol #DMT-2015.001, by any screening modality (FFDM, DBT, or SV).
- Detected at enrollment, incidentally, by any diagnostic or supplemental screening modality (HHUS or MRI).
- Detected during the annual screening interval, or at one-year follow-up (≤455 days from enrollment imaging), through diagnostic evaluation of interval symptoms, or by any diagnostic or screening modality.

Non-Cancer cases:
- Benign breast biopsy performed on lesions detected at enrollment, during the annual screening interval, or at one-year follow-up (≥ 320 days and ≤455 days from enrollment imaging) with no other lesions confirmed malignant by pathology.
- Normal or negative screening and/or diagnostic imaging at enrollment, during the annual screening interval, and at one-year follow-up (≥ 320 days and ≤455 days from enrollment imaging), with no biopsy performed.

- Normal or negative screening and/or diagnostic imaging at enrollment and during the annual screening interval, where one-year follow-up has not yet been completed, either because the annual screening interval is ongoing, or because the subject has not returned for one-year follow-up ($\geq$ 320 days and $\leq$455 days from enrollment imaging), with no biopsy performed.
- Subjects without biopsy or annual follow-up completed within 455 days of protocol screening were excluded due to lack of reference standard data.

Reader Selection

The pivotal studies (RRS2/3) included 32 MQSA-qualified radiologists who had no prior experience with the MRMC RRS study cases and had not previously participated in any of the DMT reader studies, prospective case selection study (PCC) or truthing process. The selected radiologists, whose practice involves the interpretation of digital mammograms and breast ultrasound images, included both MQSA-qualified general radiologists and subspecialist breast radiologists who completed fellowship training in breast imaging. Radiologists of any age, sex, race, ethnicity, or institutional affiliation could participate as study readers. For RRS2, more than 2,500 radiologists were invited by an IRB-approved email solicitation, 114 responded indicating their possible availability and interest to undergo qualification screening for potential participation. Thirty-two (32) readers were confirmed in order of submitting evidence of eligibility and committing to one of eight available slots in one of four sessions. The same recruitment and qualification process was followed in RRS3, with a list of invitees derived from respondents to the RRS2 solicitation who were not available to participate in any RRS2 sessions as well as new contacts who had since expressed interest in Delphinus research opportunities. Over 150 radiologists were invited, 66 responded and 32 readers were confirmed eligible and available to participate. The following criteria were used to select the readers:
- Hold a current United States medical license
- Be American Board of Radiology Certified
- Be MQSA-qualified
- Be experienced in reading FFDM images on a monitor (softcopy)
- Be experienced in reading Breast Ultrasound images on a monitor (softcopy)
- Have completed a Financial Disclosure showing no Conflicts of Interest
- Have provided a current curriculum vitae (CV)
- Have provided a signed Readers' Agreement
- Have provided written Informed Consent

Reader Training

Selected readers were required to complete a multi-module SoftVue Training program prior to participating in the reading session of the study. The training program used in RRS3 is the same as the program for the marketed product. Prior to the hands-on training, readers were required to watch a series of online training videos that provided a summary of the core concepts of the SoftVue Breast Imaging System. This independent phase of training included modules

with separate quizzes for each module to demonstrate adequate comprehension of each critical concept.

The hands-on training included individualized training from the Study PI/Peer Educator. All of the readers received a basic user training on the workstation operation and the image review functionalities prior to performing exam interpretations. The training included a review of the reading protocol, study objectives, case review process, electronic case report form (eCRF) interface and the scoring methodology. A mock practice session with the eCRF at the workstation provided the readers with an in-depth understanding of the eCRF functionality.

Additionally, a tutorial was conducted on Receiver Operating Characteristic (ROC) Analysis including the requirement for correct breast laterality localization of malignant lesions to ensure that all readers have a thorough and consistent understanding of the methodology used for lesion matching (scoring) and how their inputs will be used in data analysis. Throughout the hands-on training activity, before commencement of study case interpretations, readers were required to complete self-assessment tests, consisting of short-answer or multiple-choice written questions and/or interpretation of a mix of cases representing non-cancers, cancers, and benign lesions, which are different from the study cases. The self-assessment test results provided readers with individual feedback on their comprehension of core concepts and performance and were not utilized to advance or disqualify a reader's participation in the study.

Interpretation Procedure

Readers were set up in a darkened room that complies with industry standards, with multiple reading stations to simulate a clinical reading environment and they were required to interpret images independently of each other. Each image workstation included:

1) Two digital mammography (DM) monitors approved for review of DM,
2) A SV monitor, which uses an LCD monitor with 1920x180 pixel resolution for display of the images, and
3) A monitor for the eCRF.

Readers were permitted to magnify, pan, zoom, window/level, and perform any other specialized image viewing that they desire, beyond the default setting on the workstation. Readers were blinded to the reference standard and prospective case collection interpretations (under Protocol#DMT-2015.001) for each case. Limited patient history information that included the age, prior history of intervention, and breast laterality and location of any prior intervention for each patient, as applicable, was supplied to the readers through the "Patient History" button on the eCRF. All readers performed their interpretations independently in unique random order.

For each case, the reader first determined whether there were reportable findings on the FFDM alone and then reviewed the SV image. At no time was the

interpretation of FFDM alone allowed to be modified based upon the SV image. The SV image was only examined after the FFDM interpretation was captured and "locked". If there were no findings, the reader was asked to confirm a BI-RADS assessment category of 1 or 2; and assign a malignancy score on a scale of 0 through 100. If the reader determined there were reportable findings, the reader provided detailed information for up to 3 suspicious finding including:

- Location (including breast and view), pre-populated from the reader's annotations on the FFDM and SV workstations.
- Type, as one or more of mass, asymmetry, calcifications, architectural distortion, or other (please specify).
- Forced BI-RADS assessment category 3, 4a, 4b, 4c, or 5 for each finding.
- Malignancy score on a scale of 0 through 100 for each finding and each case

C. Study Population Demographics and Baseline Parameters

Table 8 presents a summary of the demographics of the Cancer and Non-Cancer cases identified for use in the pivotal RRS3. The majority of women were white (87%) and non-Hispanic (91%). The median age of the women in the cohort was 53.0 years old and was consistent between the cancer vs non-cancer groups. The mean height was 64.2 inches and mean weight was 147.9 lbs, resulting in a BMI of 25.2. The most frequent bra size reported was 36 (36.4%) for the group, followed by 34 (28.6%), 38 (19.3%), 32 (7.1%), 40 (4.3%) and other bra sizes (4.3%).

These data demonstrate the generalizability of the cases to the real-world population [2]. Women with dense breasts, that are identified to be at higher risk for cancer, represent more than 40% of the population [2]. The lesions identified in the cancer cases are consistent with those found in dense breast lesions [2]. Further, the sample cases of non-cancers are consistent in demographics and clinical presentation with the general population [2, 4].

Table 8: RRS3 Patient Demographics

RRS3 Patient Demographics and Clinical Characteristics			
	RRS3 Cancer Cases N=36	RRS3 Non-Cancer Cases N=104	Total N=140
Age			
Mean ± SD (N)	58.1 ± 10.8 (36)	54.7 ± 9.8 (104)	55.6 ± 10.2 (140)
Median (Min, Max)	57.0 (37.0, 84.0)	53.0 (37.0, 76.0)	53.0 (37.0, 84.0)
Race			
Asian	8.3% (3/36)	5.8% (6/104)	6.4% (9/140)
Black or African American	0.0% (0/36)	7.7% (8/104)	5.7% (8/140)

RRS3 Patient Demographics and Clinical Characteristics			
	RRS3 Cancer Cases N=36	**RRS3 Non-Cancer Cases N=104**	**Total N=140**
White or Caucasian	91.7% (33/36)	85.6% (89/104)	87.1% (122/140)
Other	0.0% (0/36)	1.0% (1/104)	0.7% (1/140)
Ethnicity			
Hispanic or Latino	11.1% (4/36)	8.7% (9/104)	9.3% (13/140)
Not Hispanic or Latino	88.9% (32/36)	91.3% (95/104)	90.7% (127/140)
Height (in)			
Mean ± SD (N)	64.9 ± 3.4 (36)	64.0 ± 3.0 (104)	64.2 ± 3.1 (140)
Median (Min, Max)	64.0 (54.0, 71.0)	64.0 (54.0, 70.0)	64.0 (54.0, 71.0)
Weight (lbs)			
Mean ± SD (N)	160.1 ± 29.8 (36)	143.6 ± 27.9 (104)	147.9 ± 29.2 (140)
Median (Min, Max)	158.5 (110.0, 258.0)	140.0 (102.0, 238.0)	144.5 (102.0, 258.0)
BMI (kg/m^2)			
Mean ± SD (N)	26.7 ± 4.6 (36)	24.7 ± 4.8 (104)	25.2 ± 4.8 (140)
Median (Min, Max)	25.2 (19.5, 38.3)	23.6 (17.0, 43.4)	24.5 (17.0, 43.4)
Bra Size			
32	2.8% (1/36)	8.7% (9/104)	7.1% (10/140)
34	16.7% (6/36)	32.7% (34/104)	28.6% (40/140)
36	33.3% (12/36)	37.5% (39/104)	36.4% (51/140)
38	33.3% (12/36)	14.4% (15/104)	19.3% (27/140)
40	5.6% (2/36)	3.8% (4/104)	4.3% (6/140)
Other	8.3% (3/36)	2.9% (3/104)	4.3% (6/140)
Bra Cup Size			
A	0.0% (0/36)	10.6% (11/104)	7.9% (11/140)
B	33.3% (12/36)	31.7% (33/104)	32.1% (45/140)
C	38.9% (14/36)	31.7% (33/104)	33.6% (47/140)
D	19.4% (7/36)	16.3% (17/104)	17.1% (24/140)

RRS3 Patient Demographics and Clinical Characteristics			
	RRS3 Cancer Cases **N=36**	**RRS3 Non-Cancer** **Cases** **N=104**	**Total** **N=140**
DD	2.8% (1/36)	6.7% (7/104)	5.7% (8/140)
Other	5.6% (2/36)	2.9% (3/104)	3.6% (5/140)
Ever Diagnosed with Breast Cancer			
Yes	5.6% (2/36)	0.0% (0/104)	1.4% (2/140)
No	94.4% (34/36)	100.0% (104/104)	98.6% (138/140)
Breast Treatments or Procedures			
Cyst Aspiration	11.1% (4/36)	9.6% (10/104)	10.0% (14/140)
Biopsy	33.3% (12/36)	19.2% (20/104)	22.9% (32/140)
Lumpectomy/Axillary Lymphadenectomy	13.9% (5/36)	0.0% (0/104)	3.6% (5/140)
Mastectomy	0.0% (0/36)	0.0% (0/104)	0.0% (0/140)
None of these	55.6% (20/36)	71.2% (74/104)	67.1% (94/140)
Still Have Natural Menstrual Periods			
Yes	30.6% (11/36)	41.3% (43/104)	38.6% (54/140)
No	47.2% (17/36)	45.2% (47/104)	45.7% (64/140)
Unknown	22.2% (8/36)	13.5% (14/104)	15.7% (22/140)
Family History of Breast Cancer			
Yes	55.6% (20/36)	51.0% (53/104)	52.1% (73/140)
No	44.4% (16/36)	48.1% (50/104)	47.1% (66/140)
Unknown	0.0% (0/36)	1.0% (1/104)	0.7% (1/140)
BRCA1 or BRCA2 Gene			
Yes	0.0% (0/36)	0.0% (0/104)	0.0% (0/140)
No	100.0% (36/36)	100.0% (104/104)	100.0% (140/140)

Table 9 shows the clinical sites included in the RRS2/3 studies as well as the number of cases used in the studies.

Table 9: Clinical Sites in RRS2/3 Studies and Number of Cases

Name	State	Number of Cancer case		Number of non-cancer cases		Total cases	
		RRS2	RRS3	RRS2	RRS3	RRS2	RRS3
University of Southern California - Keck School of Medicine (USC)	CA	18	13	29	19	47	32
Beaumont Health - Oakwood Breast Center (OAK)	MI	2	2	13	12	15	14
Weinstein Imaging Associates (WIA)	PA	5	4	26	19	31	23
Radiology Associates of the Fox Valley - St. Elizabeth Hospital Breast Center (RAFV)	WI	10	10	24	17	34	27
SouthCoast Imaging (SCI)	GA	7	5	34	23	41	28
Mount Sinai Medical Center - Lila and Howard Menowitz Breast Center (MSMC)	FL	6	2	23	14	29	16
Mercy Hospital Washington (MHW)	MO	2	0	1	0	3	0

Table 10 and **Table 11** present the readers' experience and qualifications for the readers involved in RRS2 and RRS3, respectively. The 32 readers from each study comprised a broad range of technical experience as well as clinical practice settings. In addition, the readers provided a range of geographic representation. Clinical experience of the readers ranged from 3 to 37 years in RRS2 which is consistent with RRS3 which had a range of 2

to 37 years. In addition, the readers all had extensive experience reading breast images with a median of 4800 reads/year in RRS2 and 5900 reads/year in RRS3.

Table 10: Summary of RRS2 Reader's Experience and Qualifications

RRS2 Reader's Experience and Qualifications					
Reader	Practice Category	Years in Breast Imaging	Mammography Review Rate/Year	Number of Diagnostic Breast US Reviewed in the Past Year	Number of Screening Breast US Reviewed in the Past Year
reader_2	Community Hospital	20	3000	>250 to 500	>100 to 250
reader_3	Private Practice	19	11942	>1750 to 2000	>500 to 750
reader_4	Academic	10	8000	>750 to 1000	None
reader_5	Private Practice	24	3000	>750 to 1000	>750 to 1000
reader_6	Academic	20	5000	>500 to 750	>500 to 750
reader_7	Academic	9	6000	>1250 to 1500	>1000 to 1250
reader_A	Community Hospital	9	8000	>3250 to 3500	>3250 to 3500
reader_B	Community Hospital	22	2160	>2250 to 2500	>1000 to 1250
reader_C	Academic	19	3500	>250 to 500	Less than 100
reader_D	Private Practice	18	7000	>2250 to 2500	>2500 to 2750
reader_E	Academic	6	4000	>250 to 500	None
reader_F	Private Practice	33	2100	>250 to 500	Less than 100
reader_G	Academic	10	4600	>500 to 750	None
reader_H	Academic	7	6468	>500 to 750	Less than 100
reader_I	Private Practice	15	1700	>1000 to 1250	Less than 100
reader_J	Academic	5	3430	>2250 to 2500	>100 to 250
reader_K	Private Practice	27	1200	>100 to 250	Less than 100
reader_L	Community Hospital	11	8011	>1250 to 1500	>500 to 750
reader_M	Private Practice	3	3500	>500 to 750	None

Reader	Practice Category	Years in Breast Imaging	Mammography Review Rate/Year	Number of Diagnostic Breast US Reviewed in the Past Year	Number of Screening Breast US Reviewed in the Past Year
reader_N	Community Hospital	5	5000	>2500 to 2750	>3500 to 3750
reader_O	Academic	10	8000	>1750 to 2000	>250 to 500
reader_P	Academic	7	1500	>100 to 250	Less than 100
reader_Q	Community Hospital	10	27230	>3250 to 3500	>100 to 250
reader_R	Academic	4	260	None	None
reader_S	Community Hospital	8	7737	>2500 to 2750	>100 to 250
reader_T	Community Hospital	7	6000	>1750 to 2000	Less than 100
reader_U	Community Hospital	4	5000	>2000 to 2250	Less than 100
reader_V	Private Practice	10	1200	>250 to 500	>250 to 500
reader_W	Private Practice	8	10000	More than 5000	>4250 to 4500
reader_X	Academic	19	3000	>500 to 750	>250 to 500
reader_Y	Private Practice	4	3700	>250 to 500	>250 to 500
reader_Z	Community Hospital	19	8600	>750 to 1000	Less than 100

(Table header: **RRS2 Reader's Experience and Qualifications**)

Table 1: Summary of RRS3 Reader's Experience and Qualifications

Reader	Practice Category	Years in Breast Imaging	Mammography Review Rate/Year	Number of Diagnostic Breast US Reviewed in the Past Year	Number of Screening Breast US Reviewed in the Past Year
reader_2	Academic	10	3000	>1000 to 1250	Less than 100
reader_3	Private Practice	18	10500	More than 5000	>4750 to 5000
reader_4	Private Practice	5	13360	>4750 to 5000	None

Reader	Practice Category	Years in Breast Imaging	Mammography Review Rate/Year	Number of Diagnostic Breast US Reviewed in the Past Year	Number of Screening Breast US Reviewed in the Past Year
reader_5	Academic + Community Hospital	9	9000	>1500 to 1750	None
reader_6	Private Practice	8	12100	>100 to 250	>250 to 500
reader_7	Private Practice	8	5200	>500 to 750	>100 to 250
reader_a	Private Practice	28	8354	>3250 to 3500	>3250 to 3500
reader_b	Private Practice	12	8700	>500 to 750	Less than 100
reader_c	Private Practice	10	25000	>4500 to 4750	>750 to 1000
reader_d	Private Practice	11	12000	More than 5000	>750 to 1000
reader_e	Academic + Private Practice	28	5500	>2250 to 2500	>1250 to 1500
reader_f	Community Hospital	13	4000	>750 to 1000	>100 to 250
reader_g	Academic	14	7000	>1250 to 1500	Less than 100
reader_h	Academic	11	4800	>1250 to 1500	Less than 100
reader_i	Private Practice	13	10000	>1250 to 1500	Less than 100
reader_j	Private Practice	4	14000	>1750 to 2000	>500 to 750
reader_k	Community Hospital	4	7000	>1250 to 1500	>250 to 500
reader_l	Academic	7	3816	>250 to 500	>1000 to 1250
reader_m	Community Hospital	13	6000	>2750 to 3000	Less than 100
reader_n	Private Practice	20	6000	>750 to 1000	>100 to 250
reader_o	Academic	9	5800	>1750 to 2000	>750 to 1000
reader_p	Private Practice	10	15000	>250 to 500	Less than 100
reader_q	Academic	20	1736	>500 to 750	>500 to 750
reader_r	Community Hospital	9	4000	>750 to 1000	Less than 100

Reader	Practice Category	Years in Breast Imaging	Mammography Review Rate/Year	Number of Diagnostic Breast US Reviewed in the Past Year	Number of Screening Breast US Reviewed in the Past Year
reader_s	Community Hospital	12	4000	>1250 to 1500	>1250 to 1500
reader_t	Academic + Community Hospital + Private Practice	20	4000	>1500 to 1750	Less than 100
reader_u	Private Practice + Community Hospital	23	960	>2000 to 2250	Less than 100
reader_v	Academic + Community Hospital	37	500	>100 to 250	None
reader_w	Private Practice	8	2000	>750 to 1000	>250 to 500
reader_x	Academic + Community Hospital	7	12000	>1750 to 2000	>500 to 750
reader_y	Private Practice	2	1999	>100 to 250	Less than 100
reader_z	Community Hospital	3	3600	>750 to 1000	>750 to 1000

D. Safety and Effectiveness Results

1. Safety Results

The clinical study was a Retrospective Reader Study. As such, the safety outcomes are restricted to the Interpreting Physicians (Readers) or Principal Investigator (PI). There were no adverse events reported in these individuals in the study.

2. Effectiveness Results

The analysis of effectiveness is based primarily on RRS3 which includes 140 cases with 36 cancers and 104 non-cancers. Additional analyses are provided as supportive of the product's Indications for Use.

The results were analyzed in accordance with the Statistical Analysis Plan and associated Supplement to the Statistical Analysis Plan. MRMC RRS comparison of AUCs between FFDM only and FFDM + SV was performed using the standard parametric MRMC analysis of variance (ANOVA) method of Obuchowski and Rockette (1995) to ensure generalization of the study results both to the population of readers and the population of cases [5] and also with the nonparametric MRMC analysis. We obtained the average AUC within each modality and its standard error, and the average difference in AUC for (FFDM + SV) – FFDM only and its standard error. These were used to compute corresponding two-sided 95% CIs for the average AUC within each modality and for their difference quantifying precision in these estimates.

The analysis utilized the malignancy score specified by the readers, to develop the ROC curves. The malignancy scores for use in these analyses were derived by the statistician in accordance to the prespecified algorithm as follows:
- Non-cancer case (no proven malignancies):
    - The malignancy score are the values that the reader recorded for the case (i.e., not the malignancy score for each reader-identified finding).
- Cancer case:
    - If the reader recorded findings and none of them matched the breast laterality of any proved malignant lesion, an algorithm was used to assign a value that is based upon a distribution of malignancy scores for the lowest category of Negative/Benign with malignancy score values 0-20 for the reader to the case; and the BI-RADS score for this case was assigned as category.
        - The malignancy score for any reader findings in this situation that do not match the breast laterality of any proven malignancies were ignored in the per-case analysis, which required a single malignancy score per case conditional on whether the case does or does not have proven malignancies.
    - Otherwise the malignancy score was what the reader recorded for the case (i.e., not the malignancy score for each reader-identified findings).
    - If the case contained more than one malignant lesion, the reader received credit for identifying the case as a cancer case as long as the reader identified at least one proven malignancy in the case. For example, in a bilateral case, the reader received credit for identifying the case even if the reader marked findings in only one breast.

The results for the laterality-based Primary Endpoint analyses were analyzed in accordance with the clinical study protocol and Statistical Analysis Plan (SAP).

The difference in ROC Curves between Mammography and SoftVue are averaged across the 32 Readers and is pictorially shown in **Figure 9** as the average nonparametric ROC curves. These data were used to calculate the difference in the curves using the statistical methods outlined in the SAP. **Figure 10** presents the comparison of AUC for individual readers comparing FFDM alone versus FFDM + SV.
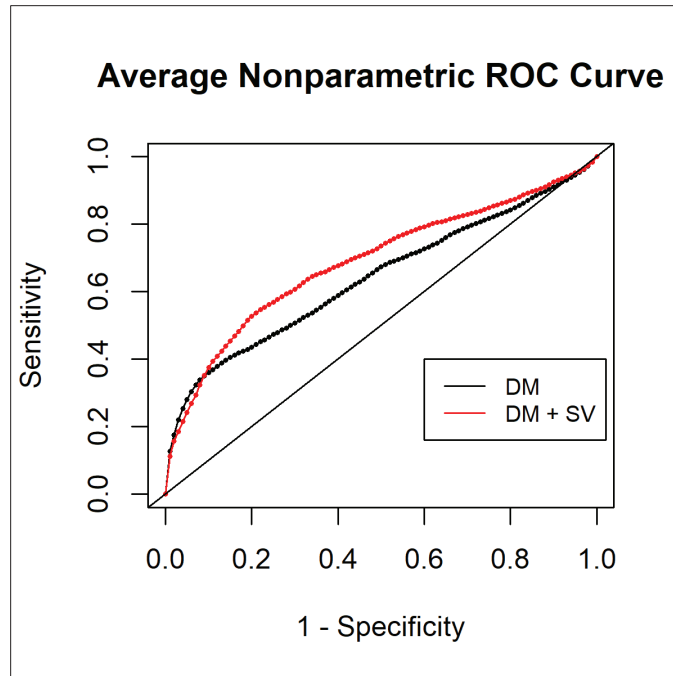
Figure 9: Average Nonparametric ROC Curve for Laterality-Based Analysis
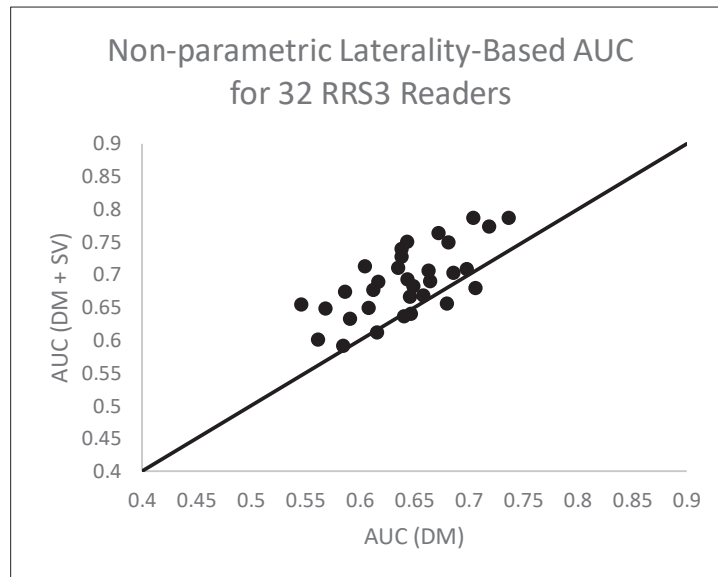

Figure 10: Reader Operating Points for 32 Readers - Nonparametric Laterally-Based Analysis

The AUC improvement values are shown in **Table 12**. As outlined by the analysis plan, both the nonparametric and parametric results were performed. However, since the ROC plots were different for the parametric versus nonparametric and the nonparametric ones are unbiased, only the nonparametric analyses are presented here. However, the p-value did not reach a level of significance for the nonparametric test for this endpoint. The sensitivity and specificity results are provided in **Table 13** for completeness. Note that

the analysis plan utilized a threshold of BI-RADS4 cases. These analyses were not required however, as the protocol and SAP require that the primary endpoint achieve significance to assess sensitivity and specificity.

Table 12: MRMC Laterality-Based Analysis of AUC using Nonparametric Approach for 32 readers in the RRS3 study and 140 cases (36 cancer, 104 non-cancer)

ROC Model	FFDM (Mean ± Standard Error)	FFDM+SV (Mean ± Standard Error)	Change from FFDM to FFDM+SV		
			ΔAUC (FFDM+SV – FFDM)	95% CI	p-value for test of superiority (two-sided alpha=0.05)
Non-parametric	0.6418 ± 0.0466	0.6897 ± 0.0415	0.0478 ± 0.0257	(-0.0025, 0.0982)	0.0624

Table 13: MRMC Laterality-Based Analysis of Sensitivity and Specificity (BI-RADS4 Threshold) for 32 readers in the RRS3 study and 140 cases (36 cancer, 104 non-cancer)

	FFDM (Mean ± Standard Error)	FFDM+SV (Mean ± Standard Error)	Change from FFDM to FFDM+SV		
			Δ Sensitivity (FFDM+SV – FFDM)	95% CI	p-value
Sensitivity	0.3837 ± 0.0654	0.4896 ± 0.0621	0.1059 ± 0.0395	(0.0285, 0.1833)	for test of superiority (two-sided alpha=0.05) 0.0073
Specificity	0.8762 ± 0.0214	0.8236 ± 0.0256	-0.0526 ± 0.0180	(-0.0878, -0.0173)	for test of non-inferiority of 10% (one-sided alpha=0.025) 0.0042

A supplemental analysis of per subject lesion localization is also provided to support the product Indications for Use. The difference in ROC Curves using a nonparametric average across all readers is provided in **Figure 11.**

Also, each individual reader performance is provided in **Figure 12,** comparing their lesion localization identification for FFDM vs FFDM + SV.
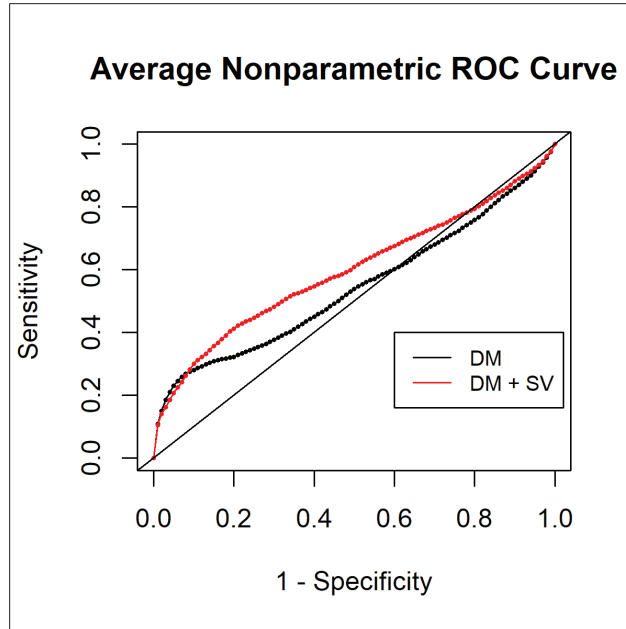
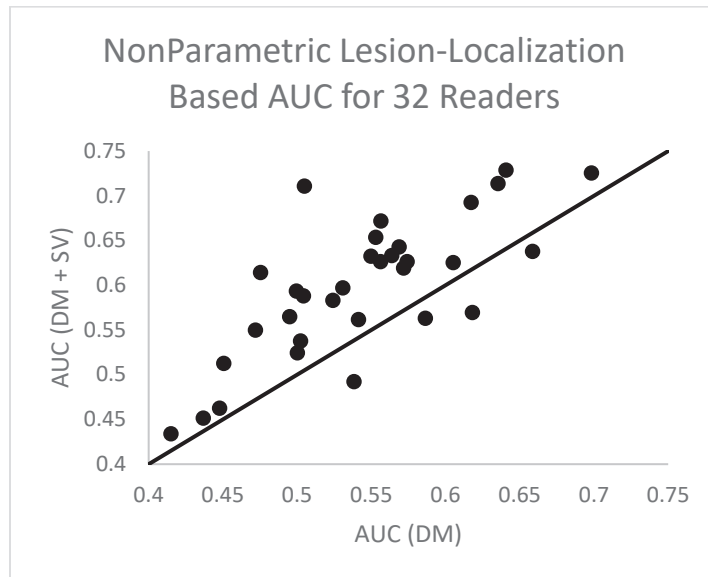**Figure 11: Average Nonparametric ROC Curve for Lesion Localization Analysis**

Figure 12: Reader Operating Points for 32 Readers – Nonparametric Based Lesion Localization Analysis

The result of this analysis, using the same statistical methodology outlined above, demonstrated a p-value of 0.0271; a significant finding (**Table 14**). As such, the sensitivity and specificity are also provided for this per subject analysis. These data provide support for the targeted, proposed indication statement and are believed to provide the relevant outcome.

Table 2: MRMC Lesion Localization-Based Analysis of AUC using Nonparametric Approach for <u>32 readers in the RRS3 study</u> and <u>140 cases</u> (36 cancer, 104 non-cancer)

ROC Model	FFDM (Mean ± Standard Error)	FFDM+SV (Mean ± Standard Error)	Change from FFDM to FFDM+SV		
			ΔAUC (FFDM+SV – FFDM)	95% CI	p-value for test of superiority (two-sided alpha=0.05)
Non-parametric	0.5436 ± 0.0489	0.5983 ± 0.0459	0.0548 ± 0.0247	(0.0062, 0.1033)	0.0271

Based upon the significant p-value identified in this supportive endpoint AUC analysis, the sensitivity and specificity were also calculated (**Table 15**) both of which are relevant since the confidence interval for sensitivity is above zero and p-values < 0.05. The results provide clinically relevant evidence supporting the proposed Indications for Use and clinical utility.

Table 15:MRMC Lesion Localization-Based Analysis of Sensitivity and Specificity (BI-RADS4 Threshold) for <u>32 readers in the RRS3 study</u> and <u>140 cases</u> (36 cancer, 104 non-cancer)

	FFDM (Mean ± Standard Error)	FFDM+SV (Mean ± Standard Error)	Change from FFDM to FFDM+SV		
			Δ Sensitivity (FFDM+SV – FFDM)	95% CI	p-value
Sensitivity	0.2977 ± 0.0636	0.3715 ± 0.0630	0.0738 ± 0.0343	(0.0066, 0.1409)	for test of superiority (two-sided alpha=0.05) 0.0314
Specificity	0.8762 ± 0.0214	0.8236 ± 0.0256	-0.0526 ± 0.0180	(-0.0878, -0.0173)	for test of non-inferiority of 10% (one-sided alpha=0.025) 0.0042

To evaluate the true clinical impact of SoftVue, a partial AUC was assessed based upon the operating point for the Readers. To identify the most appropriate operating point on the AUC curves, the sensitivity and specificity across readers was examined for both BI-RADS3 and BI-RADS4. The points identifying the range for both FFDM and FFDM + SV were used to establish the most clinically relevant operating range of (1-specificity) of 0.1 to 0.6, as shown in **Figure 13**. This range of AUC resulted in a difference of 0.0411, with a corresponding improvement in p-value of 0.0154 (**Table 16**).

Table 3: MRMC Lesion Localization-Based Analysis of Partial AUC using Nonparametric Approach for <u>32 readers from the RRS3 study</u> and <u>140 cases</u> (36 cancer, 104 non-cancer) From (1-Specificity) of 0.1 to 0.6

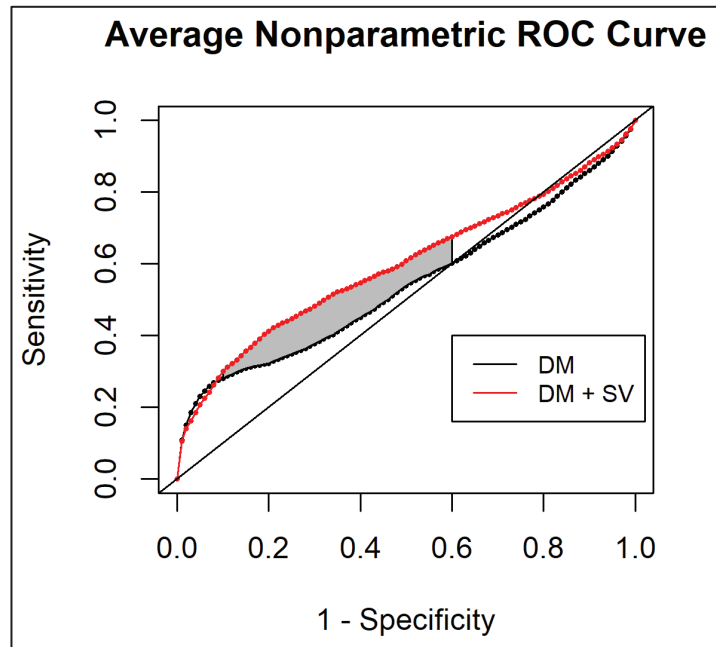| ROC Model	FFDM (Mean ± Standard Error)	FFDM+SV (Mean ± Standard Error)	Change from FFDM to FFDM+SV		
			ΔAUC (FFDM+SV – FFDM)	95% CI	p-value
Nonparametric, partial AUC	0.2134 ± 0.0308	0.2544 ± 0.0294	0.0411 ± 0.0169	(0.0079, 0.0743)	0.0154

Figure 13: Partial AUC Curve

Figures 14 and **15**, below, show the individual reader performance results as depicted on a scattergram of (1 – Specificity) vs Sensitivity for a BI-RADS3 threshold (**Figure 14**) as well as the BI-RADS4 threshold (**Figure 15**). **Figure 14** shows that when individual reader performance is evaluated for a threshold of BI-RADS3, sensitivity improves with a trend towards statistical significance (two-sided p-vlues = 0.08), and specificity improves with a statistical improvement (two-sided p-value = 0.04). This is illustrated by the shift of the FFDM performance (Dark Blue Circle) up and to the left to the SoftVue performance (Dark Orange diamond) to have an improved Sensitivity of 0.066 coincident with an improved Specificity of 0.058. This is a clinically important outcome since BI-RADS3 patients pose a particularly challenging clinical situation to physicians. The data demonstrate that with BI-RADS3 lesions, there is both increased sensitivity and increased specificity. This is especially helpful in the clinical situation of BI-RADS3 since management of these patients requires a six month wait to see if there is an increase in the size of the lesion and if so, then biopsy is indicated. In BI-RADS3 lesions, the ability to increase sensitivity with concomitant increase in specificity will allow for improvement in cancer detection without an increase in biopsy rates, particularly critical in these patients for whom the six-month wait can result in later stage diagnosis.

The performance noted for BI-RADS4 subjects (**Figure 15**) demonstrates an increase in sensitivity by 0.074 (two-sided p-value = 0.03) when Softvue was combined with mammography, as noted by the shift upwards from the Dark Blue Circle to the Dark Orange Diamond. This improved sensitivity was at a tradeoff in decreased specificity by 0.053) which is not unexpected. Since the BI-RADS4 subjects have a higher likelihood of cancer, the increase in potential biopsies is anticipated and this tradeoff is considered reasonable.
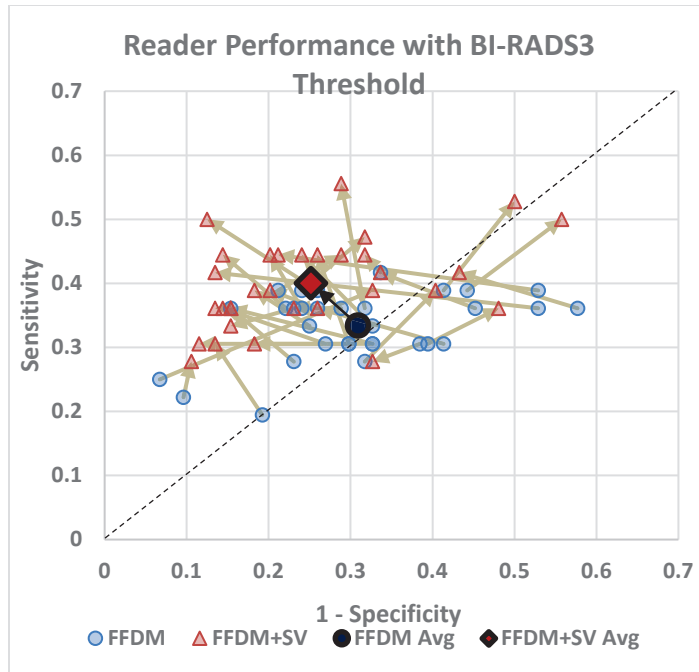
Figure 14: Individual Reader Performance Threshold BI-RADS3: Average Reader Performance from FFDM (Dark Blue Circle) to FFDM with SV (Dark Orange Diamond) illustrate the improvement in both Sensitivity and Specificity when BI-RADS3 case threshold are analyzed.
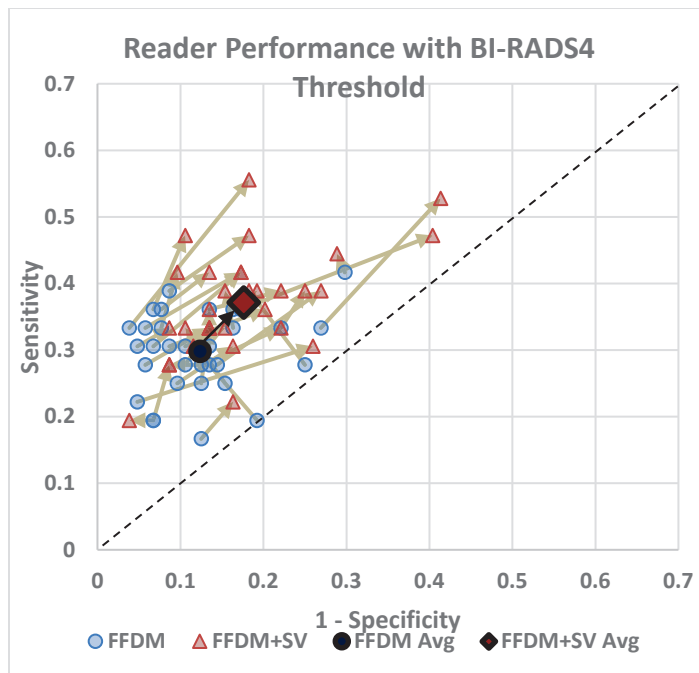

Figure 15*: Individual Reader Performance Threshold BI-RADS4: Average Reader Performance from FFDM (Dark Blue Circle) to FFDM with SV (Dark Orange Diamond) illustrate the improvement in Sensitivity (to 0.372) with a decrease in Specificity (to 0.824) when BI-RADS4 case threshold are analyzed.

Summary of Supplemental Clinical Information

The RRS3 study provides the pivotal data on AUC improvement, sensitivity and specificity of SoftVue as a screening tool in comparison with digital mammography. Based upon the original SAP, the improvement in AUC was measured as 5.48% absolute improvement over mammography which corresponds to a relative improvement of +10.08% which is statistically significant with a two-sided p-value of 0.0271.

This AUC improvement corresponds with an absolute Sensitivity improved of 7.38% which is associated with a relative improvement of +24.79%. This improvement in sensitivity is balanced by a Specificity decrement of 5.26% which corresponds with a 6.00% relative decrement.

In addition, a partial AUC curve targeted around the operating region of the readers was determined based upon the actual reader performance. This result improved the p-value on SoftVue performance to 0.0154.

Additional evaluation of the reader performance as a supplemental analysis was performed based on a threshold of BI-RADS3 in addition to a BI-RADS4 threshold to provide a comprehensive presentation of the study results. When individual reader performance was evaluated for a threshold of BI-RADS3, both sensitivity (+6.66%, two-sided p-value = 0.08) and specificity (+5.77%, two-sided p-value = 0.04)) are improved. The average individual performance results with a BI-RADS4 threshold demonstrated an increase in Sensitivity (+7.38%, two-sided p-vlaue = 0.03) with a decrease in Specificity (-5.26%) which is the tradeoff typically noted in AUC performance clinical studies.

The summary of study results is provided in **Table 17** below.

Table 4: RRS3 Clinical Study Results

Study	% Relative Change ([FFDM+SV – FFDM alone]/FFDM alone)	Δ (FFDM+SV – FFDM alone)	95% Confidence Interval
Δ AUC – Laterality			
Primary Analysis	7.45%	0.0478	(-0.0025, 0.0982)
Δ AUC - Lesion Localization			
Supportive Analysis	10.08%	0.0548	(0.0062, 0.1033)
Partial Δ AUC - Lesion Localization			
Supportive Analysis	19.26%	0.0411	(0.0079, 0.0743)
Δ Sensitivity – Laterality (BI-RADS4 Threshold)			
Primary Analysis of Secondary Endpoint	27.60%	0.1059	(0.0285, 0.1833)

Δ Sensitivity – Lesion Localization (BI-RADS4 Threshold)			
Supportive Analysis	24.79%	0.0738	(0.0066, 0.1409)
Δ Specificity (BI-RADS4 Threshold)			
Primary Analysis of Secondary Endpoint	-6.00%	-0.0526	(-0.0878, -0.0173)
Δ Sensitivity – Lesion Localization (BI-RADS3 Threshold)			
Supportive Analysis	19.75%	0.0660	(-0.0085, 0.1404)
Δ Specificity (BI-RADS3 Threshold)			
Supportive Analysis of Secondary Endpoint	8.35%	0.0577	(0.0034, 0.1120)

As noted in **Table 17** above, screening mammography with SoftVue can enhance the ability of clinicians to identify suspicious breast lesions in patients with dense breasts. Lesion localization is a key outcome to support the intended use of SoftVue. Based on the results of RRS3, screening mammography with SoftVue provided an increase in sensitivity (lesion localization based) and an increase in specificity for those cases with BI-RADS3, a positive both for sensitivity and specificity, but a decrease for BI-RADS4 which is not unexpected since most modalities require additional biopsies to detect additional cancers. These data support the proposed clinical indication for the product and supports the overall risk to benefit ratio of SoftVue being added to screening mammography to address the limitations of mammography in dense breast patients.

3. Peditric Extrapolation

Not Applicable

E. **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 68 investigators in total for the three RRS studies. 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

All clinical information have been summarized above.

XII. 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 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the clinical studies show that SofVue System provide a reasonable assurance of safety and effectiveness for the intended use of the device, and the specified indications for use.

The results show that screening mammography with SoftVue can enhance the ability of clinicians to identify suspicious breast lesions in patients with dense breasts. Lesion localization is a key outcome to support the intended use of SoftVue. Based on the results of RRS3, screening mammography with SoftVue provided an increase in sensitivity (lesion localization based) and an increase in specificity for those cases with BI-RADS3, a positive both for sensitivity and specificity, but a decrease for BI-RADS4 which is not unexpected since most modalities require additional biopsies to detect additional cancers.

B. Safety Conclusions

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

C. Benefit-Risk Determination

The probable benefits of the SoftVue System as an adjunct to mammography outweigh the risks. The device provides an effective method of breast cancer screening for asymptomatic dense-breasted women.

The probable risks of the SoftVue System are in terms of diagnostic accuracy, e.g., false positives and false negatives. A false positive test would lead to additional imaging evaluation that would otherwise not be performed. The additional workup would result in increased expense and anxiety for the patient and risk of additional discomfort and

potential complications such as infection resulting from biopsy. The consequences of a false negative would be delay in diagnosis, which would happen if the SoftVue System were not used in the first place, as the target patient population are women who have dense breasts, and are asymptomatic.

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, given the available information above, the data support that for the indication for use of the device the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support a reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results of the Pivotal studies demonstrate that the SoftVue System is safe and effective as an adjunct to mammography for breast cancer screening in women with dense breast parenchyma (BI-RADS® density composition c or d).

XIV. CDRH DECISION

CDRH issued an approval order on 10/06/2021.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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