SOFTVUE™ 3D WHOLE BREAST ULTRASOUND TOMOGRAPHY SYSTEM (SOFTVUE™) PHYSICIAN LABELING

Contact Information

Delphinus Medical Technologies, Inc. welcomes comments, questions, and suggestions in an effort to offer patients and health care professionals the best imaging tool for screening and diagnostic use. Please contact us:

E-mail (Preferred)
info@delphinusmt.com

By Telephone (For time sensitive matters)
In the USA: +1 (844) SOFTVUE (+1 (844) 763-8883)

By Mail
Delphinus Medical Technologies, Inc.
45525 Grand River Avenue
Novi, MI 48374

On The Web
www.delphinusmt.com

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MANUFACTURER

Delphinus Medical Technologies, Inc.
45525 Grand River Avenue
Novi, MI 48374
U.S.A.

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Chapter 1 Prescription Use Statement

Federal law restricts this device to sale to or on the order of a physician. The use of this device is restricted to those who receive the appropriate training.

Chapter 2 Indication for Use Statement

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.

Chapter 3 Contraindications, Warnings, and Precautions

3.1 Contraindications

There are no known contraindications for the use of the SoftVue™ System

3.2 Warnings and Precautions

The warnings and precautions for the SoftVue™ System can be found in the User Manual.

Chapter 4 Clinical Study Summary

The Delphinus Pivotal Retrospective Reader Study (DMT-2019.002) [RRS3] was an analysis of radiologist [Reader] image interpretation performance utilizing prospectively collected patient data obtained from an independent multi-center Prospective Case Collection Registry (DMT-2015.001) [PCC Registry]. The patient data utilized in RRS3 was collected from a total of six (6) PCC Registry clinical sites across the U.S. The retrospective analysis performed is an observational case-controlled, multi-reader, multi case [MRMC] Receiver Operating Characteristic (ROC) study involving 32 Readers who were MQSA qualified radiologists with experience in breast image interpretation. The cases were comprised of bilateral full-field digital mammography [FFDM] and SoftVue (SV) screening imaging acquired from the same patient during the same screening interval. There were one hundred and forty (140) cases sampled for the Pivotal RRS3 study from a pool of 7,439 asymptomatic female volunteers with BI-RADS c or d breast density, of which thirty-six (36) were proven by pathology to have breast cancer, five (5) were biopsy proven benign lesions, and ninety-nine (99) were confirmed non-cancer after one year of follow-up with normal or negative bilateral mammographic imaging.

The primary endpoint analysis was based on a comparison of a Reader's image assessment for a digital screening mammogram alone (FFDM Alone) vs. the same Reader's image

assessment for the same digital screening mammogram paired with a screening SoftVue (SV) exam from the same patient (FFDM+SV). Using the area under the ROC (AUC) averaged across Readers, performance with FFDM alone compared to performance with FFDM + SV was evaluated as a primary objective, where calculation of AUC required that the reader identify the correct breast laterality for malignant lesions. As a secondary objective, the sensitivity and specificity for FFDM Alone vs. FFDM+SV was calculated and averaged across readers, also requiring correct breast laterality of malignant lesions for sensitivity and a non-inferiority margin delta = 0.10 for specificity. Additionally, in order to evaluate reader performance within a context relevant to how SoftVue™ is intended to be used in actual clinical practice, a supportive analysis of both objectives was performed requiring correct lesion localization within 1.5cm of the cancer biopsy site for AUC and sensitivity. The cancer biopsy site was determined as the area encompassing the locations mapped by a panel of three radiologists. The results of the Pivotal RRS3 are summarized below and demonstrate the safety and effectiveness of SoftVue™ to enhance the screening process in patients with dense breasts to identify suspicious lesions that would benefit from further diagnostic assessment for breast cancer.

Prior to participating as Readers in the Pivotal RRS, each reader completed Delphinus' SoftVue Radiologist Training Curriculum. Equivalent training is required for prescription use of the device. Both trainings consist of self-study video training modules with conceptual testing, as well as hands-on case review training delivered by a physician experienced in SV image interpretation. A self-assessment test is administered to provide users with feedback on their SV interpretation performance after completing the training curriculum. No readers were excluded based upon the self-assessment outcome. All readers scored above 80%.

During the Pivotal RRS3, each reader interpreted each of the one hundred and forty (140) cases in a unique random order, blinded to the ground truth (cancer vs. non-cancer). For each case, a Reader first interpreted the FFDM Alone, without access to the SV images, using commercially available equipment to display the medical images in a setting that simulated standard practice. Suspicious findings (if any) were marked on the FFDM images. A BI-RADS® assessment category was provided and a malignancy score between 1 and 100 was assigned for FFDM Alone. Upon completing the FFDM alone interpretation, the Reader reviewed the SV exam together with FFDM. Suspicious findings (if any) were marked on the FFDM and SV images, a BI-RADS® assessment category was provided and a malignancy score between 1 and 100 was assigned for FFDM+SV. The primary endpoint was the difference in the reader-averaged area under the ROC curve (AUC) between the FFDM Alone reading and the FFDM+SV reading. A secondary endpoint was the Reader-averaged sensitivity and specificity for FFDM+SV reading compared to FFDM Alone reading.

A complete summary of the RRS3 Endpoint Results is provided below.

4.1 Safety Results

Since this is a Retrospective Reader Study, 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.

4.2 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.

4.2.1 Primary Endpoint Results

The results were analyzed in accordance with a Statistical Analysis Plan (SAP) and associated Supplement to the Statistical Analysis Plans. 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)[1] to ensure generalization of the study results both to the population of readers and the population of cases and also with the non-parametric 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.

4.3 Results – RRS3

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

The difference in ROC Curves between Mammography and SoftVue™ is averaged across the 32 Readers and is pictorially shown in Figure 1 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 2 presents the comparison of AUC for individual readers comparing FFDM alone versus FFDM + SV.

[1] Obuchowski NA, R.H., Hypothesis testing of diagnostic accuracy for multiple readers and multiple tests: An ANOVA approach with dependent observations. Commun Stat SImul Comput, 1995. 24: p. 285-308.

Figure 1: Average Nonparametric ROC Curve for Laterality-Based Analysis

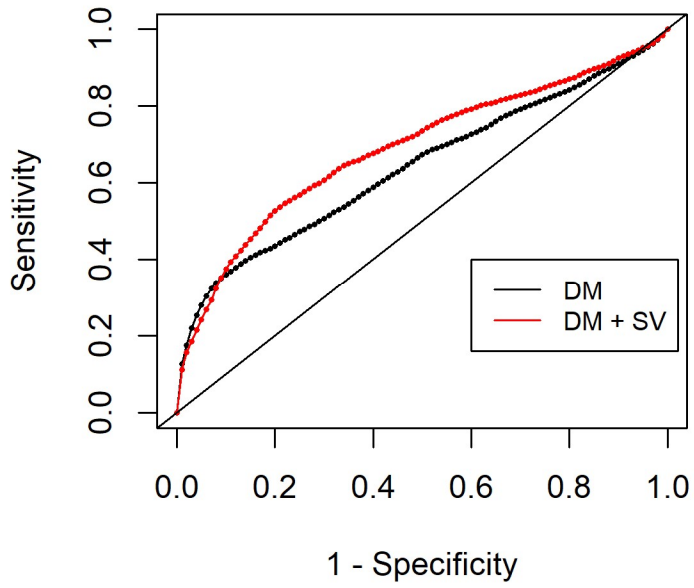
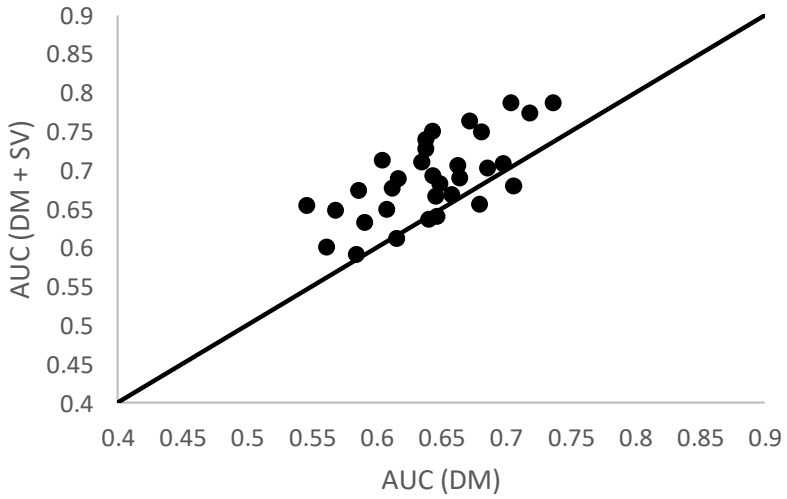


Figure 2: Reader Operating Points for 32 Readers - Nonparametric Laterality-Based Analysis



4.3.1 Primary Endpoint Results – Laterality

The AUC improvement values are shown in Table 1. As outlined by the analysis plan, both the non-parametric and parametric results were performed. However, since the ROC plots were so different for the parametric versus non-parametric and the nonparametric ones are unbiased, only the non-parametric analyses are presented here. The p-value did not reach a level of significance for the non-parametric test for this endpoint, however. The sensitivity and specificity results are provided in Table 2 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 1: MRMC Laterality-Based Analysis of AUC using Non-parametric 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 2: MRMC Laterality-Based Analysis of Sensitivity and Specificity (BI-RADS 4 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

4.3.2 Supplemental Analyses Based on Indications for Use and Clinical Utility

Lesion Localization – RRS3

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 non-parametric average across all readers is provided in Figure 3. Further, each individual reader performance is provided in Figure 4, comparing their lesion localization identification for FFDM vs FFDM + SV.

Figure 3: Average Nonparametric ROC Curve for Lesion Localization Analysis

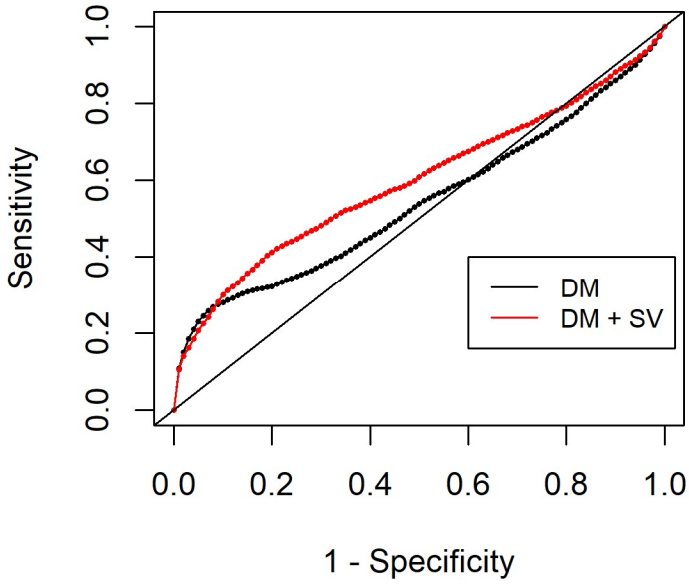
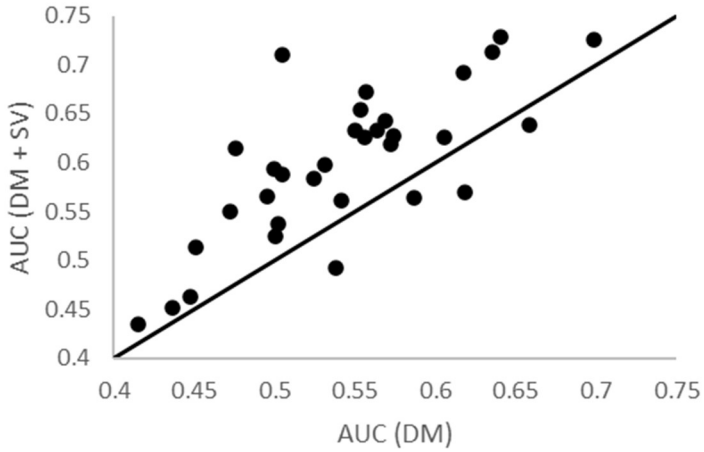


Figure 4: Reader Operating Points for 32 Readers – Nonparametric Based Lesion Localization Analysis



The result of this analysis, using the same statistical methodology outlined above, demonstrated a p-value of 0.0271; a significant finding (Table 3). 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 3: MRMC Lesion Localization-Based Analysis of AUC using Non-parametric 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	0.5436 ± 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 4); 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 4: MRMC Lesion Localization-Based Analysis of Sensitivity and Specificity (BI-RADS 4 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	0.2977 ± 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

Lesion Localization – Partial AUC Analysis

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 were 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 5. This range of AUC resulted in a difference of 0.0411, with a corresponding improvement in p-value of 0.0154 (Table 5).

Figure 5: Partial Average Nonparametric AUC Curve

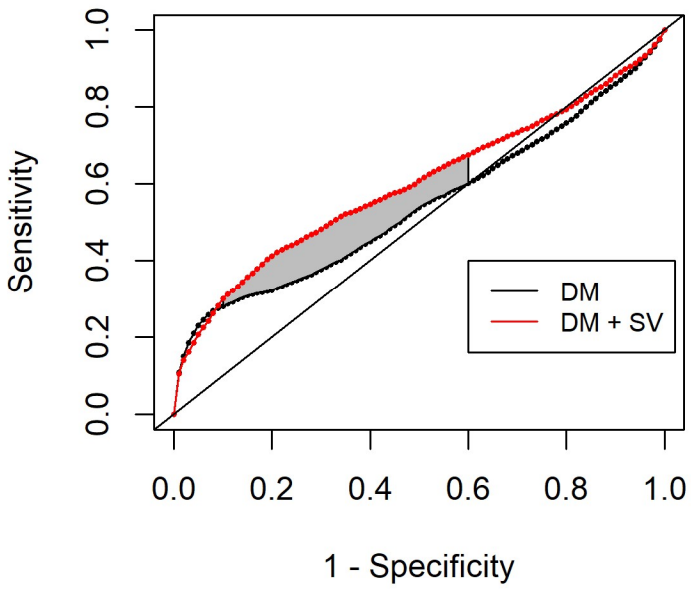


Table 5: MRMC Lesion Localization-Based Analysis of Partial AUC using Non-parametric Approach for 32 readers from the RRS3 study and 140 cases (36 cancer, 104 non-cancer) From (1-specificity) of 0.1 to 0.6

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
Non-parametric, partial AUC	0.2134 ± 0.0308	0.2544 ± 0.0294	0.0411 ± 0.0169	(0.0079, 0.0743)	0.0154

Additional evaluation of the reader performance based on a threshold of BI-RADS3 is considered as a supplemental analysis in addition to a BI-RADS4 threshold to provide a comprehensive presentation of the study results. Figure 6 and Figure 7 show the individual reader performance results as depicted on a scattergram of (1 – specificity) vs. Sensitivity for a BI-RADS3 threshold (Figure 6) as well as the BI-RADS4 threshold. Figure 6 shows that when individual reader performance is evaluated for a threshold of BI-RADS3, sensitivity improves with a trend towards significance and strikingly, specificity improves with a statistical improvement (two-sided p=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 improved the sensitivity by 0.066 (two-sided p=0.08) coincident with improved specificity by 0.058 (two-sided p=0.04). This is a clinically important outcome since BI-RADS 3 patients pose a particularly challenging clinical situation to physicians. The data demonstrate that with BI-RADS 3 lesions, there is both increased sensitivity and increased specificity as the curve moves up and to the left. This is especially helpful in the clinical situation of BIRADS 3 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-RADS 3 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.

Figure 6: Individual Reader Performance Threshold BI-RADS 3: Average Reader Performance from FFDM (Dark Blue Circle) to FFDM with SV (Dark Orange Diamond) illustrate the improvement in both Sensitivity (0.066, two-sided p=0.08) and Specificity (0.058, two-sided p=0.04) when BI-RADS3 case threshold are analyzed

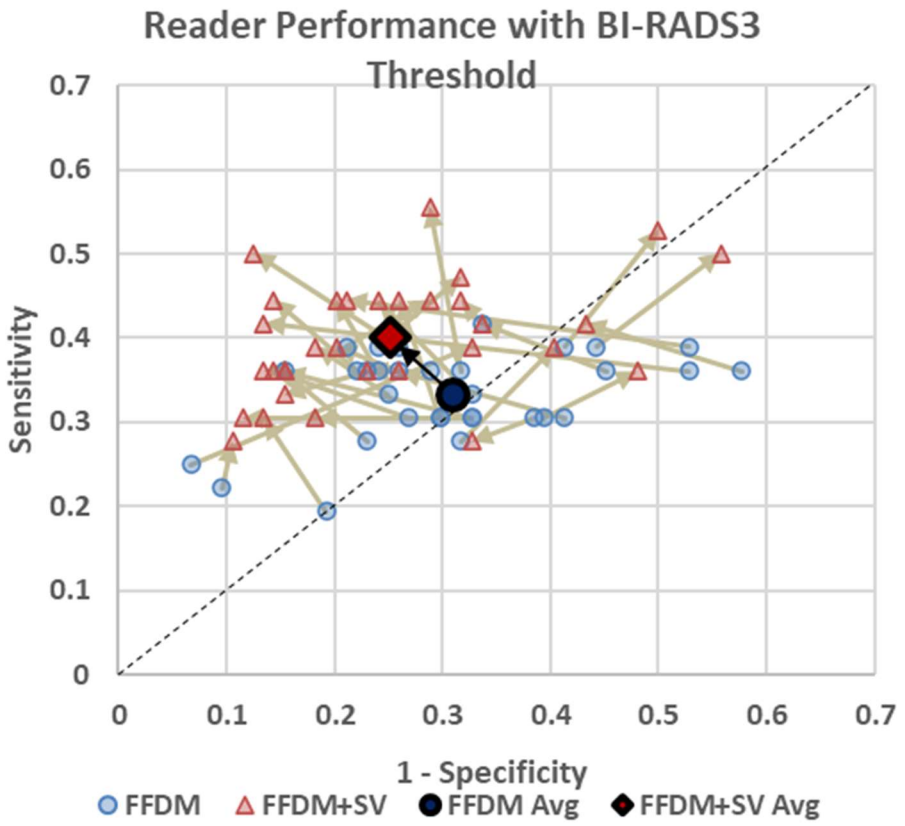
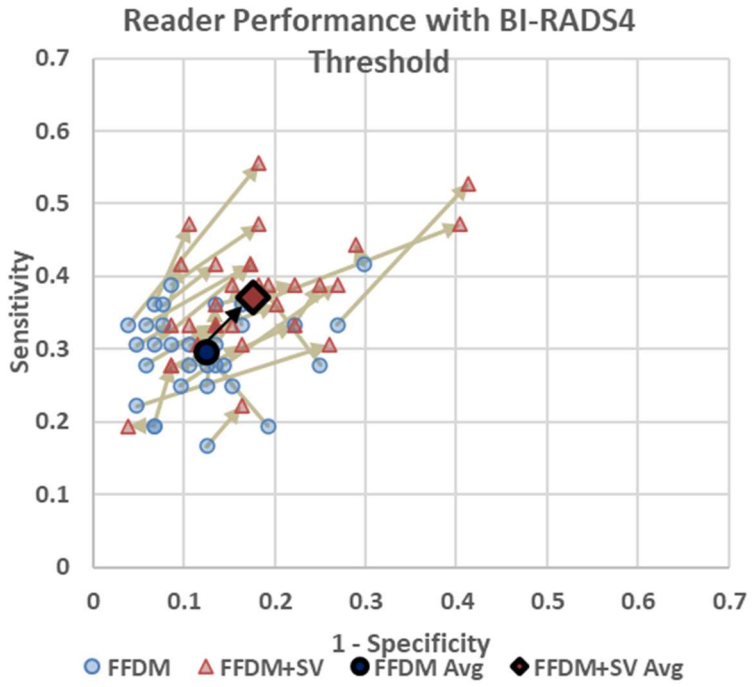


Figure 7: Individual Reader Performance Threshold BI-RADS 4: Average Reader Performance from FFDM (Dark Blue Circle) to FFDM with SV (Dark Orange Diamond) illustrate the improvement in Sensitivity (0.074, two-sided p=0.03) with a decrease in Specificity (0.053) when BI-RADS4 case threshold are analyzed



The performance noted for BI-RADS 4 subjects (Figure 7) demonstrates an increase in sensitivity by 0.074 (two-sided p=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.

Chapter 5 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 two-sided p-value on SoftVue performance to p=0.0154.

Additional evaluation of the reader performance as a supplemental analysis was performed based on a threshold of BI-RADS 3 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=0.08) and specificity (+5.77%, two-sided p=0.04) are improved. The average individual performance results with a BI-RADS4 threshold demonstrated an increase in Sensitivity (+7.38%, two-sided p=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 6.

Table 6: 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-RADS 4 Threshold)			
Primary Analysis of Secondary Endpoint	27.60%	0.1059	(0.0285, 0.1833)
Δ Sensitivity – Lesion Localization (BI-RADS 4 Threshold)			
Supportive Analysis	24.79%	0.0738	(0.0066, 0.1409)
Δ Specificity (BI-RADS 4 Threshold)			
Primary Analysis of Secondary Endpoint	-6.00%	-0.0526	(-0.0878, -0.0173)
Δ Sensitivity – Lesion Localization (BI-RADS 3 Threshold)			
Supportive Analysis	19.75%	0.0660	(-0.0085, 0.1404)

Study	% Relative Change ([FFDM+SV – FFDM alone]/FFDM alone)	Δ (FFDM+SV – FFDM alone)	95% Confidence Interval
Δ Specificity (BI-RADS 3 Threshold)			
Supportive Analysis of Secondary Endpoint	8.35%	0.0577	(0.0034, 0.1120)

As noted in Table 6, 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 support the overall risk to benefit ratio of SoftVue™ being added to screening mammography to address the limitations of mammography in dense breast patients.