CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203684Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 203-684 No. 21
Drug Name:	Lumason (Sulfur Hexafluoride) Microbubbles Injection
Indication(s):	Lumason is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification (LVO) and improve endocardial border delineation (EVD).
Applicant:	Bracco Diagnostics Inc.
Date(s):	NDA Original Submission: December 21, 2011 Complete Response (CR) Letter on October 19, 2012 Resubmission: May 31, 2013 PDUFA Date: November 30, 2013 Complete Response (CR) Letter in November, 2013 Resubmission: April 11, 2014 PDUFA Date: October 11, 2014
Review Priority:	Priority
Biometrics Division:	Division of Biostatistics V
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Team Leader Tom Gwise, Division Deputy Director
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Scheldon Kress, M. D. Clinical TL: Alex Gorovets, M. D.
Project Manager:	Frank Lutterodt

Memorandum to file

No Action Intended for NDA 203-684 - Lumason

NDA Number: 203-684

Sponsor: Bracco Diagnostics, Inc.

Drug: Lumason (Sulfur Hexafluoride) Microbubbles Injection

Dosage form and route of administration: Lyophilized powder for reconstitution and intravenous (IV) injection

Dosing regimen: (b) (4)

Propose Indication: For use in echocadiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation (EBD).

Lumason (sulfur hexafluoride, SF-6) is intended for use as an echocardiographic (ECHO) imaging agent for patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation (EBD).

The NDA received a Complete Response (CR) Letter on October 19, 2012 due to facility inspection deficiencies. The sponsor (applicant) resubmitted the NDA for approval in May 2013. Due to continued compliance deficiencies, a regulatory meeting was held and a request for additional information was sent to the sponsor in November 2013. A Complete Response (CR) was subsequently issued for NDA 203684 in November 2013. Additional compliance information from the sponsor was provided in December, 2013. In April, 2014 Bracco Diagnostics Inc. resubmitted the application for review with a PDUFA date of 11-Oct-2014. This application is now complete and approvable.

Labeling was mostly done before re-submission. Clinical and Statistical section of the label (PI) are not changed and no new clinical data were submitted since the first cycle review. The statistical report is documented in DARRTS (NDA 203-684 Statistical Review for SonaVue (now Lumason)) dated September 17, 2012.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SATISH C MISRA
09/18/2014

JYOTI ZALKIKAR
09/18/2014
I concur with the primary reviewer.

THOMAS E GWISE
09/25/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 203-684
Drug Name:	SonoVue™(Sulfur Hexafluoride) Microbubbles Injection
Indication(s):	SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification (LVO) and improve endocardial border delineation (EVD).
Applicant:	Bracco Diagnostics Inc.
Date(s):	NDA Original Submission: December 21, 2011 Complete Response (CR) Letter on October 19, 2012 Resubmission: May 31, 2013 PDUFA Date: November 30, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biostatistics V
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Team Leader
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Scheldon Kress, M. D. Clinical TL: Alex Gorovets, M. D.
Project Manager:	Frank Lutterodt

Memorandum to file

No Action Intended for NDA 203-684 - SonaVue

NDA Number: 203-684

Sponsor: Bracco Diagnostics, Inc.

Drug: SonoVue (sulfur hexafluoride) Microbubbles

Dosage form and route of administration: Lyophilized powder for reconstitution and intravenous (IV) injection

Dosing regimen: (b) (4)

Propose Indication: For use in echocardiography (ECHO) in patients with suboptimal ECHO, to obtain left ventricular opacification and improve endocardial border delineation (EBD).

SonoVue (sulfur hexafluoride, SF-6) is intended for use as an echocardiographic (ECHO) imaging agent for patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation (EBD).

The NDA received a Complete Response (CR) Letter on October 19, 2012 due to facility inspection deficiencies. The sponsor (applicant) resubmitted the NDA for consideration of approval in May 2013.

PI was mostly done before re-submission. The main items remaining were as follows: (1) Updating the proprietary name and (2) Updating the safety information. The new proposed name is Lumason (formerly SonoVue) which is an ultrasound contrast agent characterized by a microbubble structure consisting of a low solubility gas, sulfur hexafluoride (SF6), stabilized by a phospholipid shell. Lumason is presented as a kit consisting of Lumason powder for dispersion vial and a Lumason solvent for dispersion pre-filled syringe. Lumason powder for injection is a 25 mg sterile, non-pyrogenic lyophilized powder in a (b) (4)-sealed vial. Clinical and Statistical section of the PI are not changed and no new clinical data were submitted since the first cycle review. The statistical report is documented in daarts -- NDA 203-684 Review Stat SonaVue dated September 17, 2012.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SATISH C MISRA
10/10/2013

JYOTI ZALKIKAR
10/10/2013
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 203-684 Supplement 00
Drug Name:	SonoVue™(Sulfur Hexafluoride) Microbubbles Injection
Indication(s):	SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification (LVO) and improve endocardial border delineation (EVD).
Applicant:	Bracco Diagnostics Inc.
Date(s):	NDA Submission: December 21, 2011 PDUFA Date: October 19, 2012
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Biometrics Division:	Division of Biostatistics V
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Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Scheldon Kress, M. D. Clinical TL: Alex Gorovets, M. D. Medical Division Director: Dwaine Rieves, M. D.
Project Manager:	Frank Lutterodt

Keywords: : Clinical Studies, Blinded, Control, Cardiac, Contrast, Ultrasound

Comment – dropped tests of hypotheses related to comparing with control. All p-values comparing to control are dropped. Basic statistics are kept in the table to give a picture of the very poor performance of the control.

Reference ID: 3189315

Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES **1**

FOOD AND DRUG ADMINISTRATION **1**

STATISTICAL REVIEW AND EVALUATION **1**

LIST OF TABLES **3**

1. EXECUTIVE SUMMARY **4**

2. INTRODUCTION **6**

2.1 OVERVIEW 6
2.1.1 Indication and Dosage *7*
2.1.2 Identified Studies in the review *7*
2.1.3 Patient Population *7*
2.1.4 Safety Patient Population *8*
2.2 DATA SOURCES 8

3. STATISTICAL EVALUATION **9**

3.1 DATA AND ANALYSIS QUALITY 9
3.2 EVALUATION OF EFFICACY 9
3.2.1 Study Design, Objectives and Endpoints *9*
3.2.2 Statistical Methodologies *10*
3.2.3 Demographic and Baseline Characteristics *11*
3.2.4 Results and Conclusions *13*
3.3 EVALUATION OF SAFETY 20

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **21**

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 21

5. SUMMARY AND CONCLUSIONS **23**

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 23
5.2 CONCLUSIONS AND RECOMMENDATIONS 24

SIGNATURES/DISTRIBUTION LIST **25**

Reference ID: 3189315

LIST OF TABLES

Table 1: Endocardial border delineation score 4
Table 2: Overview of Clinical Studies 7
Table 3: Demographics and Baseline Characteristics Demographic and Baseline Characteristics 12
Table 4: Baseline and Change from Baseline for Endocardial border delineation score 14
Table 5: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-019A 16
Table 6: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-019B 17
Table 7: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-013 18
Table 8: Percentage of Patients With LV Opacification Scores of +2 or +3 19
Table 9: Comparison of Pre (Baseline) vs Post (Sonovue Enhanced) LVEBD Scores 20
Table 10: Percent of Suboptimal Baseline Reads for which Enhanced Reads are Adequate 20
Table 11: Segment by Segment Comparison of Dose vs. Baseline Suboptimal Reads for LVEBD 20
Table 12: Analysis by Gender 21
Table 13: Analysis by Race 22
Table 14: Analysis by Age 22
Table 15: Endocardial border delineation score 24

Reference ID: 3189315

1. EXECUTIVE SUMMARY

SonoVue™ (sulfur hexafluoride microbubbles) injection is an ultrasound drug product (intravenously administered suspension) indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. The sponsor stated that the drug product has been approved for European market for several years, IV use currently approved in 36 countries for Opacification of cardiac chambers, Enhance left ventricular endocardial border delineation, etc.

Three adequate and well-controlled studies (BR1-019A, BR1-019B, and BR1-013) were identified and formed the basis for the evaluation of efficacy of SonoVue for EBD and LVO. These studies were single blind (subject blinded to identity and dose of agents administered), parallel-group comparisons of SonoVue and Albunex. Preinjection and postinjection echocardiographic images for each patient were evaluated by two off-site blinded, independent echocardiographers unaffiliated with any of the investigational sites of the study. All blinded reads followed a prospectively designed blinded read methodology.

Primary Efficacy Evaluation is based on Left Ventricular Endocardial Border Delineation (LVEBD) (typical for the Cardiovascular trials). The LVEB is partitioned into 12 Apical viewable segments (apical 4-chamber view and apical 2-chamber view). Each segment is scored as: 0 if inadequately delineated (border not visible); 1 if sufficiently delineated (border barely visible) ; 2 if well delineated (border clearly visible). LVEBD is then defined as the sum over all the segments, and ranges from 0 to 24.

Improvements in LVEBD for Sonovue Enhanced Echo Images over Baseline is the primary focus. Primary endpoint is Mean increase from baseline for the SonoVue group.

Mean baseline (preinjection) and mean change from baseline for total left ventricular border delineation score are summarized in Table 1 for the 3 confirmatory studies

Table 1: Endocardial border delineation score

	Study BR1-019A			Study BR1-019B			Study BR1-013		
Reader A*	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change
Dose SonaVue(mL)									
0.5	75	7.2	4.6	62	8.9	3.8		--	--
1.0	76	7.9	4.7	62	8.9	3.9	53	12.0	4.6
2.0	76	7.5	7.0	62	9.0	5.1	53	11.9	3.6
4.0	75	7.5	7.1	62	8.7	5.0		--	--
Reader B*									
Dose SonaVue(mL)									
0.5	76	6.7	8.8	62	4.6	13.4	--	--	--
1.0	76	8.0	8.8	61	4.6	16.2	53	6.3	4.1
2.0	76	7.6	9.6	62	4.6	17.2	53	6.7	4.5
4.0	76	7.2	10.7	62	4.2	18.2	--	--	--

* Different readers in each of the three studies.

** # of patients who had both the pre- and postinjection image evaluation at each dose

Reference ID: 3189315

Left Ventricle Opacification (LVO) Scores is defined as:

-1 Non-Diagnostic Images
0 None (no visible contrast)
1 Faint (weak or trace effect of contrast within left ventricle0
+2 moderate (some areas of the left ventricle fully opacified but without a time when whole cavity is filled with contrast of the same high intensity)
+3 complete (homogeneous, high intensity contrast effect)

Across all off-site readers, opacification scores of +2 or +3 were recorded for more than 70% of patients in all SonoVue dose groups, and more than 85% of patients in the 2-mL and 4-mL dose groups.

Dr. A. Mucci of the Division of Biostatistics provided statistical support and performed extensive statistical analysis for the NDA submitted in 2001. Dr. A. Mucci's and this reviewer's analyses provide adequate evidence to support the proposed indication for SonoVue.

Reference ID: 3189315

2. INTRODUCTION

Bracco submited an original NDA 203-684 for SonoVue™ (sulfur hexafluoride microbubbles) injection. SonoVue is an ultrasound contrast indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. The sponsor stated that the drug product has been approved for European market for several years, IV use currently approved in 36 countries for Opacification of cardiac chambers, Enhance left ventricular endocardial border delineation, etc.

2.1 Overview

A brief regulatory history is given below:

A previous NDA (# 21-315) was submitted to the FDA on January 21, 2001 in support of a similar indication for use in visualization of the endocardial border (b) (4)

The sponsor was invited to present SonoVue US safety data to CRDAC in 2008. A meeting was held with DMIP to explore re-submission in 2009. In this meeting it was agreed that the primary database could rely on 3 prior confirmatory studies.

FDA also recommended to complete pulmonary hemodynamic study prior to NDA submission, and retrospective observational study among critically ill patients. In 2011 CRDAC reviewed the safety of USC agents and concerns raised regarding validity of retrospective studies, limitations of premier database & propensity score analyses as well as absence of significant pulmonary hemodynamic effects by USCA. Bracco requested guidance from FDA (going forward). In a 2011 meeting with FDA produced the following agreements:

- Retrospective observational study no longer required prior to submission of NDA.
- Results of pulmonary hemodynamic study (BR1-133) can be submitted with NDA.
- NDA can be submitted for use in echocardiography with indication for LVO (Left Ventricular Opacification) and EBD (Endocardial Border Delineation). (Optison & Definity have similar indication approvals)

Sponsor submitted an original NDA with focus on agreed upon indication (LVO - Left Ventricular Opacification and EBD - Endocardial Border Delineation). There were no new data in this submission. The data submitted in 2001 were submitted again. These data were analyzed by Dr. Anthony Mucci and his report is available in darrts. The focus of this review is limited to the agreed upon indication and three pivotal studies.

The aims of clinical development program included determining the optimal dose of SonoVue for endocardial border delineation through provision of adequate and prolonged opacification of the left ventricular cavity; comparing the diagnostic performance of SonoVue to that of a control agent (Albunex and/or saline) in the delineation of the ventricular border; and evaluating the effectiveness of SonoVue in improving the delineation of the endocardial border in patients with suspected cardiac disease and suboptimal unenhanced echocardiography.

Reference ID: 3189315

2.1.1 Indication and Dosage

SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification (LVO) and improve endocardial border delineation (EVD).

The recommended dose of SonoVue™ for left ventricular opacification and endocardial border delineation is 2 mL administered as an intravenous bolus injection during echocardiography. During a single examination, a second injection of 2 mL may be administered when deemed necessary. Each SonoVue injection should be followed by a flush with 5 ml of sodium chloride injection (0.9% w/v), USP.

2.1.2 Identified Studies in the review

As agreed in communications with the Division of Medical Imaging Product, the 3 confirmatory studies (BR1-019A, BR1-019B, and BR1-013) form the basis for the evaluation of efficacy of SonoVue for EBD and LVO, since these are adequate and well-controlled studies.

Results from two prospective Phase II/III studies in 437 patients with known or suspected cardiac disease (BR1-011, BR1-012) provide supportive evidence for the indication Summary details of the study protocols for the efficacy studies and the numbers treated under each are provided.

An overview of 3 confirmatory clinical studies is given in the following Table 2:

Table 2: Overview of Clinical Studies

Confirmatory Studies: ***Suspected cardiac disease and suboptimal border delineation on unenhanced echocardiography***					
BR1-019A Phase II/III	143 76 (67)[a]	Single-blind, parallel-comparative, crossover-dose ranging	0.5, 1.0, 2.0, 4.0 mL	Albunex 0.9% Saline	0.08 mL/kg 0.22 mL/kg 0.08 mL/kg 0.22 mL/kg
BR1-019B Phase II/III	121 62 (59)[a]	Single-blind, parallel-comparative, crossover-dose ranging	0.5, 1.0, 2.0, 4.0 mL	Albunex 0.9% Saline	0.08 mL/kg 0.22 mL/kg 0.08 mL/kg 0.22 mL/kg
BR1-013 Phase II/III	53 53 (53)[a]	Single-blind, crossover	1.0, 2.0 mL	Albunex	0.22 mL/kg
Total	**317** **191 (179)**[a]				

[a] Number of patients who received SonoVue (number of patients who received control).

2.1.3 Patient Population

Three confirmatory studies (BR1-019A, BR1-019B, and BR1-013) form the basis for the evaluation of efficacy of SonoVue for EBD and LVO. The patients enrolled in these studies are those with suspected cardiac disease and suboptimal border delineation on unenhanced 2D echocardiography at rest and reflect patients receiving ultrasound contrast in current clinical practice and those currently recommended for contrast echocardiography by international professional societies including the American Heart Association (AHA), the American College of Cardiology, and the American Society of Echocardiography (ASE).

Reference ID: 3189315

Inclusion Criteria were:

- Suspected cardiac disease (≥18 years age)
- Suboptimal LV EBD (none-contrast ECHO)
    - Minimum EBD score ≥ 4/12 regions
    - Total EBD score ≤ 14/24

Major Exclusion Criteria were:

- Severe CHF
- Recent myocardial infarction
- Unstable angina
- Serious arrhythmia
- Severe pulmonary hypertension
- Known hypersensitivity
- Pregnant or lactating

The imaging protocols for all three confirmatory studies were identical (details provided in the clinical report).

2.1.4 Safety Patient Population

The safety profile for SonoVue has been extensively documented in both clinical trial settings and during post-marketing surveillance, since SonoVue is approved in 36 countries world-wide and marketed in 25 countries world-wide. The safety population consisted of cumulative database of the clinical trials conducted in North America, Europe, and Asia.

2.2 Data Sources

The submission has a mixture of text based and scanned PDF files. The majority of the documents scanned PDF documents. The NDA was submitted in eCTD format and contained SAS export files for the confirmatory studies. Analysis datasets for safety and efficacy including derived datasets were provided in xpt format. Study reports from prior submissions were also included. Additional effort was needed to derive the useful analyses datasets from the provided data.

The NDA in eCTD and SAS export files of these data are located at:
\\CDSESUB1\EVSPROD\NDA203684\

Reference ID: 3189315

3. STATISTICAL EVALUATION

The focus of statistical evaluation of efficacy of SonoVue for EBD and LVO is the 3 adequate and well-controlled confirmatory studies (BR1-019A, BR1-019B, and BR1-013) as agreed with the Agency.

3.1 Data and Analysis Quality

A previous NDA (# 21-315) was submitted to the FDA on January 21, 2001 in support of a similar indication for use in visualization of the endocardial border. These data were evaluated by Dr. Anthony Mucci of the Office of Biostatistics and documented in darrts. The sponsor submitted the current NDA (# 203-684) as an original submission with the same data and analyses for focused indication per agreement with FDA. The original submission included (b) (4) The focus of this review is limited to the agreed upon indication and three pivotal studies.

3.2 Evaluation of Efficacy

3.2.1 Study Design, Objectives and Endpoints

Study Design

The confirmatory studies were multicenter trials that employed an active control (Albunex, the only ultrasound contrast agent approved in the United States at the time of the trials) and/or a placebo control (saline).

Phase III Confirmatory Studies BR1-019A, and BR1-019B were identically designed, parallel-group comparisons of SonoVue and Albunex. The studies were conducted in 11 and 10 studies centers, respectively. The studies were single-blind (subject blinded to identity and dose of agents administered) because differences in volume and color of the administered agents and doses made it impractical to maintain investigator blinding. In each study, one-half of the patients enrolled were randomly assigned to receive 4 doses of SonoVue, 0.5, 1, 2, and 4 mL (approximately 0.007, 0.014, 0.03, and 0.06 mL/kg in a 70-kg [body weight] person), according to one of 4 randomized dose sequences; and one-half were assigned to receive 2 doses of Albunex, 0.08 and 0.22 mL/kg, and 2 doses of agitated saline at volumes equal to the Albunex dose volumes, according to 1 of 4 randomized dose sequences. Albunex, the comparator of interest, was administered at the 2 recommended doses, with agitated saline administered to balance the dosing to maintain the blind. Subjects were randomized to study agent (SonoVue or Albunex) and then randomly assigned to one of 4 different dose sequences.

Phase III Confirmatory Study BR1-013 was a multicenter (6 centers), single-blind (patient-blinded), randomized, crossover study of SonoVue and Albunex. Each patient received 2 doses of SonoVue, 1 mL and 2 mL (approximately 0.01 and 0.03 mL/kg in a 70-kg person), and 1 dose of Albunex (0.22 mL/kg). Subjects were randomly assigned to one of 3 different sequences of study agent administration.

Preinjection and postinjection echocardiographic images for each patient were evaluated by two off-site blinded, independent echocardiographers unaffiliated with any of the investigational sites of the study. All blinded reads followed a prospectively designed blinded read methodology.

Objectives

The primary objectives of the studies were to determine the optimal efficacious dose and efficacy for SonoVue based on the primary endpoint of Left ventricle (LV) endocardial border delineation (EBD) – LVEBD and the secondary endpoint of LV opacification (LVO) for inclusion in the indication statement.

Important secondary endpoints included duration of useful contrast enhancement and Wall Motion.

Reference ID: 3189315

Primary Endpoint

The Primary Efficacy Endpoint for all three studies was Left Ventricular Endocardial Border Delineation (LVEBD) which was measured, principally, as a sum of visibility scores over all the segments constituting the Apical border. This Endocardial Border score was assumed to be representative of an overall level of Apical Endocardial Border "visibility".

The study was designed to compare the product to a control. The FDA medical team advised that the active control Albunex (used in all three studies) is no longer used routinely for Echocardiography, therefore the emphasis of this statistical review with respect to the primary efficacy endpoint will be on direct comparisons of Sonovue Enhanced Echo LVEBD to Baseline Echo LVEBD, to determine if Sonovue images provided greater LVEBD visibility than did baseline, and which dose level achieved the best such visibility differential.

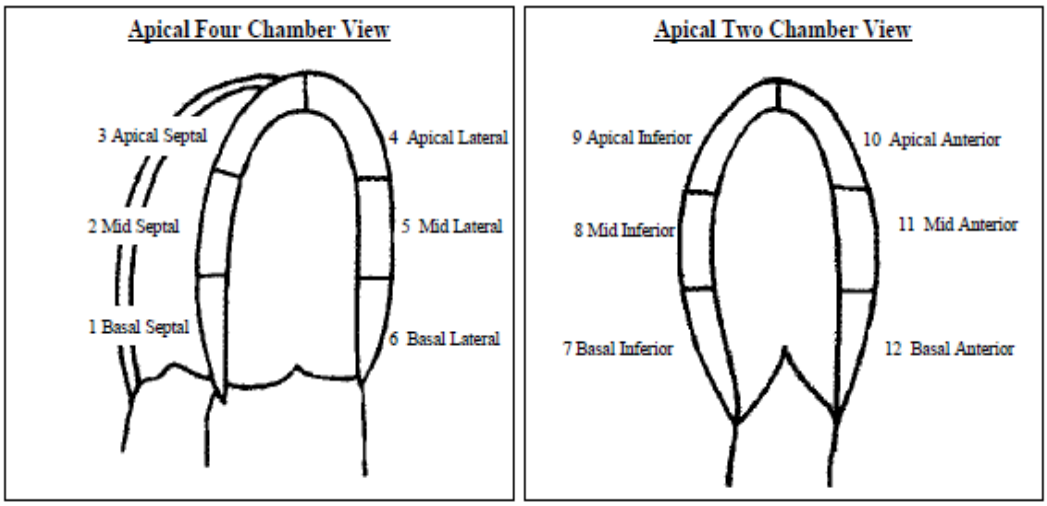
LVEBD is the primary focus in the analysis and is consistent with the proposed indication. The change from baseline in total LV EBD score for the SonoVue studies was prospectively defined and agreed upon with the FDA.

3.2.2 Statistical Methodologies

Endocardial Border Delineation (EBD) Score

In these studies, a segment-specific EBD score was utilized, and the left ventricle was divided into the standardized six segments (one basal, one middle, and one apical segment of each wall) according to the guidelines defined by the American Society of Echocardiography and used in routine clinical practice in the Untied States and abroad (Figure 1).

Figure 1. Apical Four-Chamber and Two-Chamber Views for Assessment of EBD and LVO in Studies BR1-019A, BR1-019B and BR1-013 (Sponsor)



The LVEB is partitioned into12 Apical viewable segments (apical 4-chamber view and apical 2-chamber view). Endocardial border delineation for each segment was graded using the following scale:

0 = Inadequate (border not visible)
+1 = Sufficient (border barely visible)
+2 = Good (border clearly visible)

Reference ID: 3189315

LVEBD is then defined as the sum over all the segments, and ranges from 0 to 24.

Left Ventricle Opacification (LVO)

Degree of left ventricle opacification following each injection was graded according to the following four-point rating scale:

-1 = non-diagnostic
0 = none, no visible contrast within the left ventricular cavity
+1 = faint, weak or trace effect of contrast within the left ventricle
+2 = moderate, some areas of the left ventricle fully opacified but without a time when the whole cavity is filled with contrast to the same high intensity
+3 = complete, homogeneous and high intensity effect.

3.2.3 Demographic and Baseline Characteristics

A summary of patient demographics and baseline characteristics for the three confirmatory studies combined is presented in Table 3. Of the 191 patients who received SonoVue in these studies (including patients who received both SonoVue and Albunex in study BR1- 013), 66.5% were male and 33.5% were female. Of the 179 patients who received control agents, 71.5% were male and 28.5% were female. The majority of patients in both study agent groups were white (SonoVue 79.1%; control 77.7%). Ages in the SonoVue group ranged from 22 to 96 years (mean age, 58.5 years). Ages in the control group ranged from 23 to 96 years (mean age, 60.0 years). Approximately 21% of patients had a pulmonary disorder at baseline (chronic bronchitis, emphysema, or asthma) altogether in both SonoVue and control groups. Twenty-eight percent (28%) of patients who received SonoVue and 34% of patients who received control had NYHA Class II/III heart disease.

Reference ID: 3189315

Table 3: Demographics and Baseline Characteristics Demographic and Baseline Characteristics (Confirmatory Studies for Endocardial Border Delineation by Study (Sponsor))

Parameter	BR1-019A		BR1-019B		BR1-013[b]
	SonoVue N=76	Control[a] N=67	SonoVue N=62	Control[a] N=59	N=53
Gender, n (%)					
Male	50 (65.8)	46 (68.7)	39 (62.9)	44 (74.6)	38 (71.7)
Female	26 (34.2)	21 (31.3)	23 (37.1)	15 (25.4)	15 (28.3)
Age (yrs)					
18-64, n (%)	50 (65.8)	44 (65.7)	42 (67.7)	33 (55.9)	26 (49.1)
≥65, n (%)	26 (34.2)	23 (34.3)	20 (32.3)	26 (44.1)	27 (50.9)
Mean	56.7	58.1	56.8	59.4	63.2
Range	22 - 81	23 - 79	29 - 77	26 - 80	29 - 96
Race, n (%)					
White	63 (82.9)	51 (76.1)	49 (79.0)	49 (83.1)	39 (73.6)
Black	13 (17.1)	11 (16.4)	9 (14.5)	5 (8.5)	9 (17.0)
Other	0	5 (7.5)	4 (6.4)	5 (8.5)	5 (9.4)
Weight (kg)					
Mean	98.4	93.8	89.4	94.3	88.9
Range	52 - 184	48 - 216	42 - 165	51 - 181	48 - 173
Pulmonary disorder, n (%)[c]					
Yes	16 (21.1)	9 (13.4)	11 (17.7)	12 (20.3)	14 (26.4)
No	60 (78.9)	58 (86.6)	51 (82.3)	47 (79.7)	39 (73.6)
Previous heart failure, n (%)					
No	60 (78.9)	52 (77.6)	45 (72.6)	33 (55.9)	28 (52.8)
Yes	16 (21.1)	15 (22.4)[d]	17 (27.4)	26 (44.1)	25 (47.2)
NYHA Class I	3 (3.9)	3 (4.5)	3 (4.8)	4 (6.8)	5 (9.4)
NYHA Class II	11 (14.5)	7 (10.4)	6 (9.7)	9 (15.3)	11 (20.8)
NYHA Class III	2 (2.6)	4 (6.0)	8 (12.9)	13 (22.0)	9 (17.0)

a Albunex/saline
b Patients received both SonoVue and control (Albunex) doses in a crossover design.
c Patients with chronic bronchitis, emphysema, or asthma based on blinded medical review of general medical history and physical examination data recorded at screening.
d One patient in the control group had previous heart failure noted on the CRF, but NYHA class was not provided.
Data source: studies BR1-019A, BR1-019B, and BR1-013 clinical trial reports and analyses of the data.

Reference ID: 3189315

3.2.4 Results and Conclusions

3.2.4.1 The primary efficacy endpoint - Endocardial border delineation score

Mean baseline (preinjection) and mean change from baseline for total left ventricular border delineation score are summarized for the 3 confirmatory studies in Table 4. Across all off-site readers in studies BR1-019A and BR1-019B, mean change from baseline scores for the SonoVue group ranged from 3.8 to 18.2 (across all four doses), while mean change from baseline scores for the control group ranged from -0.2 to 4.3. For all four off-site reviewers, the mean increase from baseline was statistically significant for all four SonoVue doses ($p<0.001$; t-test). For each of the off-site readers, the change from baseline in endocardial border delineation score tended to increase with increasing SonoVue dose, with a tendency to plateau between the 2-mL and 4-mL doses, as shown in Figure 2.

In studies BR1-019A and BR1-019B, mean change from baseline scores for SonoVue differed among the four off-site, blinded readers, with ranges of 3.8 to 5.1 (BR1-019B, Reader A), 4.6 to 7.1 (BR1-019A, Reader A), 8.8 to 10.7 (BR1-019A, Reader B), and 13.4 to 18.2 (BR1- 019B, Reader B) across the four dose levels (Table 4). Some of the differences among readers may be due to differences at baseline; the reader with the lowest baseline scores showed the greatest increase with SonoVue administration and vice versa. Such differences were not unexpected due to inherent differences in the scoring approaches of the off-site readers. The observed differences in the grading of images with respect to border delineation may reflect individual differences in diagnostic threshold, leading to a more or less conservative definition of ‘visualization’, i.e., clearly diagnostic versus readable.

Reference ID: 3189315

Table 4: Baseline and Change from Baseline for Endocardial border delineation score

	Study BR1-019A			Study BR1-019B			Study BR1-013		
Reader A*	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change
Dose SonaVue(mL)									
0.5	75	7.2	4.6	62	8.9	3.8		--	--
1.0	76	7.9	4.7	62	8.9	3.9	53	12.0	4.6
2.0	76	7.5	7.0	62	9.0	5.1	53	11.9	3.6
4.0	75	7.5	7.1	62	8.7	5.0		--	--
Control (mL/Kg)									
Saline 0.08	66	7.8	-0.1	58	8.2	0.1	--	--	--
0.22	67	7.8	0.3	58	8.3	0.3	--	--	--
Albunex 0.08	66	7.6	0.8	58	8.3	0.1	--	--	--
0.22	66	7.3	2.0	58	8.6	0.4	5.3	11.8	0.4
Reader B*									
Dose SonaVue(mL)									
0.5	76	6.7	8.8	62	4.6	13.4	--	--	--
1.0	76	8.0	8.8	61	4.6	16.2	53	6.3	4.1
2.0	76	7.6	9.6	62	4.6	17.2	53	6.7	4.5
4.0	76	7.2	10.7	62	4.2	18.2	--	--	--
Control (mL/Kg)									
Saline 0.08	67	8.1	-0.2	58	4.2	-0.2	--	--	--
0.22	66	7.4	0.6	58	3.8	0.1	--	--	--
Albunex 0.08	66	7.4	1.9	58	4.4	2.4	--	--	--
0.22	66	6.9	3.1	58	4.3	4.3	5.3	--	--

Total score is the sum of scores of the apical 4-chamber view and apical 2-chamber view. Each view consists of 6 segments. Scores for each segment are as follows:

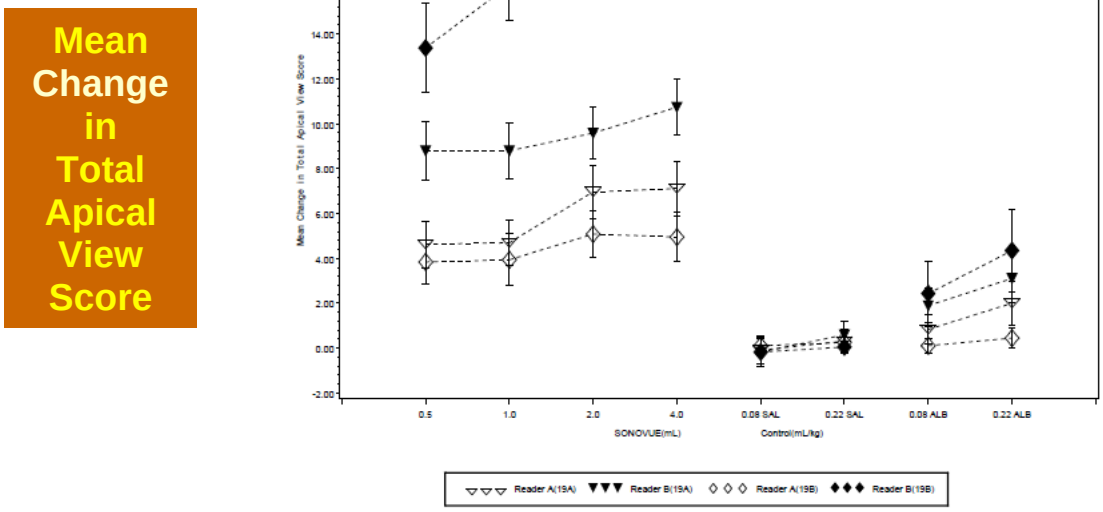
Score: 0 = Inadequate (border not visible);
+1 = Sufficient (border barely visible);
+2 = Good (border clearly visible).

* Different readers in each of the three studies.

** # of patients who had both the pre- and post-injection image evaluation at each dose

Reference ID: 3189315

Figure 2: Left Ventricle Endocardial Border Delineation,
Mean Change From Baseline in Total Apical View Score by Study Agent
Off-site Image Evaluation - Studies 019A and 019B (Sponsor)



Mean Change in Total Apical View Score

3.2.4.2 Left Ventricle Opacification (LVO) Score

LVO was evaluated in the 3 confirmatory studies. For BR1-019A and -019B, LVO was a primary endpoint; in BR1-013, LVO was a secondary endpoint.

As shown in Table 5 and Table 6, for all four off-site readers in studies BR1-019A and - 019B, opacification scores were significantly higher for each of the four doses of SonoVue compared with the maximum opacification scores in the control group ($p<0.001$; Wilcoxon rank-sum test). A dose-response in left ventricle opacification was evident in the SonoVue group, and in the control group for the two Albunex doses. For both off-site readers in study BR1-013, the difference in opacification scores between SonoVue and Albunex was statistically significant ($p<0.001$; Wilcoxon signed-rank test) for both doses of SonoVue (Table 7).

The percentage of patients with opacification scores of +2 (moderate) or +3 (complete) and the percentage of patients with opacification scores of +3 is presented in Table 8 for all study agent groups in the three confirmatory studies. Across all off-site readers, opacification scores of +2 or +3 were recorded for more than 70% of patients in all SonoVue dose groups, and more than 85% of patients in the 2-mL and 4-mL dose groups.

Reference ID: 3189315

Table 5: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-019A

			Non-Diagnostic	No. (%) of Patients with LV Opacification Score			
Reader			-1	0	+1	+2	+3
Study Agent	Dose	N[a]	n (%)	n (%)	n (%)	n (%)	n (%)
Reader A							
SonoVue(mL)							
	0.5	75	12 (16)	0	2 (3)	15 (20)	46 (61)
	1.0	76	11 (15)	0	3 (4)	12 (16)	50 (66)
	2.0	76	7 (9)	0	3 (4)	5 (7)	61 (80)
	4.0	75	5 (7)	0	0	6 (8)	64 (85)
Control(mL/kg)							
Saline	0.08	66	25 (38)	38 (58)	3 (5)	0	0
	0.22	67	31 (46)	31 (46)	2 (3)	1 (2)	2 (3)
Albunex	0.08	66	25 (38)	9 (14)	13 (20)	15 (23)	4 (6)
	0.22	66	23 (35)	7 (11)	15 (23)	12 (18)	9 (14)
Maximum Response[b]		67	12 (18)	8 (12)	16 (24)	18 (27)	13 (19)
Reader B							
SonoVue(mL)							
	0.5	76	6 (8)	0	8 (11)	36 (46)	26 (34)
	1.0	76	3 (4)	0	8 (11)	31 (41)	34 (45)
	2.0	76	3 (4)	0	8 (11)	22 (29)	43 (57)
	4.0	76	4 (5)	0	2 (3)	28 (37)	42 (55)
Control(mL/kg)							
Saline	0.08	67	16 (24)	43 (64)	8 (12)	0	0
	0.22	67	14 (21)	49 (73)	3 (5)	1 (2)	0
Albunex	0.08	66	13 (20)	15 (23)	25 (38)	10 (15)	3 (5)
	0.22	66	10 (15)	7 (11)	24 (36)	21 (32)	4 (6)
Maximum Response[b]		67	7 (10)	8 (12)	24 (36)	22 (33)	6 (9)

a Includes patients who had postinjection image evaluations at each dose.
b The maximum score (-1 to +3) for each patient among the four doses summarized for the control group. The difference between the two agents (SonoVue minus maximum response in the control group) is significant using a Wilcoxon rank-sum test.
Source: Sponsor's table N (Study BR1-019B clinical trial report).

Reference ID: 3189315

Table 6: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-019B

			Non-Diagnostic	No. (%) of Patients with LV Opacification Score			
Reader			-1	0	+1	+2	+3
Study Agent	Dose	N[a]	n (%)	n (%)	n (%)	n (%)	n (%)
Reader A							
SonoVue(mL)							
	0.5	62	14 (23)	0	3 (5)	23 (37)	22 (36)
	1.0	62	10 (16)	0	0	26 (42)	26 (42)
	2.0	62	7 (11)	0	0	23 (37)	32 (52)
	4.0	62	7 (11)	0	0	20 (32)	35 (57)
Control(mL/kg)							
Saline	0.08	58	19 (33)	38 (66)	1 (2)	0	0
	0.22	58	16 (28)	40 (69)	2 (3)	0	0
Albunex	0.08	58	17 (29)	21 (36)	11 (19)	9 (16)	0
	0.22	58	14 (24)	12 (21)	18 (31)	14 (24)	0
Maximum Response[b]		58	5 (9)	19 (33)	18 (31)	16 (28)	0
Reader B							
SonoVue(mL)							
	0.5	62	9 (15)	2 (3)	4 (7)	8 (13)	39 (63)
	1.0	61	4 (7)	0	6 (10)	7 (12)	44 (72)
	2.0	62	2 (3)	0	5 (8)	6 (10)	49 (79)
	4.0	62	3 (5)	0	2 (3)	3 (5)	54 (87)
Control(mL/kg)							
Saline	0.08	58	35 (60)	23 (40)	0	0	0
	0.22	58	33 (57)	25 (43)	0	0	0
Albunex	0.08	58	29 (50)	14 (24)	7 (12)	5 (9)	3 (5)
	0.22	58	21 (36)	11 (19)	11 (19)	6 (10)	9 (16)
Maximum Response[b]		58	12 (21)	18 (31)	12 (21)	5 (9)	11 (19)

a Includes patients who had postinjection image evaluations at each dose.
b The maximum score (-1 to +3) for each patient among the four doses summarized for the control group. The difference between the two agents (SonoVue minus maximum response in the control group) is significant using a Wilcoxon rank-sum test.
Source: Sponsor's table O (Study BR1-019B clinical trial report).

Reference ID: 3189315

Table 7: Left Ventricle Opacification Score, Off-site Image Evaluation - Study BR1-013

Reader Study Agent	Dose	N[a]	No. (%) of Patients with LVOpacificationScore 0 n (%)	+1 n (%)	+2 n (%)	+3 n (%)	p-value[b]
Reader A							
Albunex	0.22 mL/kg	53	19 (35.8)	20 (37.7)	13 (24.5)	1 (1.9)	
SonoVue	1.0 mL	53	1 (1.9)	3 (5.7)	22 (41.5)	27 (50.9)	< 0.001
	2.0 mL	53	2 (3.8)	2 (3.8)	20 (37.7)	29 (54.7)	< 0.001
Reader B							
Albunex	0.22 mL/kg	53	19 (35.8)	21 (39.6)	13 (24.5)	0	
SonoVue	1.0 mL	53	1 (1.9)	1 (1.9)	16 (30.2)	35 (66.0)	< 0.001
	2.0 mL	53	1 (1.9)	1 (1.9)	13 (24.5)	38 (71.7)	< 0.001

a Includes patients who had both pre- and postinjection image evaluations at each dose.
b The within-group difference between the two agents (SonoVue minus Albunex) tested using the Wilcoxon signed-rank test.
Source: Sponsor's table P (study BR1-013 clinical trial report.)

Reference ID: 3189315

Table 8: Percentage of Patients With LV Opacification Scores of +2 or +3

Reader Study Agent	Dose	BR1-019A N[a]	BR1-019A Score of +2 or +3	BR1-019A Score of +3	BR1-019B N[b]	BR1-019B Score of +2 or +3	BR1-019B Score of +3	BR1-013 N[b]	BR1-013 Score of +2 or +3	BR1-013 Score of +3
Reader A[b]										
SonoVue(mL)										
	0.5	75	81%	61%	62	73%	36%		---	---
	1.0	76	82%	66%	62	84%	42%	53	92%	51%
	2.0	76	87%	80%	62	89%	52%	53	92%	55%
	4.0	75	93%	85%	62	89%	57%		---	---
Control(mL/kg)										
Saline	0.08	66	0%	0%	58	0%	0%		---	---
	0.22	67	4%	3%	58	0%	0%		---	---
Albunex	0.08	66	29%	6%	58	16%	0%		---	---
	0.22	66	32%	14%	58	24%	0%	53	26%	2%
Maximum response[c]		67	46%	19%	58	28%	0%		---	---
Reader B[b]										
SonoVue(mL)										
	0.5	76	82%	34%	62	76%	63%		---	---
	1.0	76	86%	45%	61	84%	72%	53	96%	66%
	2.0	76	86%	57%	62	89%	79%	53	96%	72%
	4.0	76	92%	55%	62	92%	87%		---	---
Control(mL/kg)										
Saline	0.08	67	0%	0%	58	0%	0%		---	---
	0.22	67	2%	0%	58	0%	0%		---	---
Albunex	0.08	66	20%	5%	58	14%	5%		---	---
	0.22	66	38%	6%	58	26%	16%	53	25%	0%
Maximum response[c]		67	42%	9%	58	28%	19%		---	---

a Number of patients with postinjection image evaluations at each dose.
b Represents different individuals in each of the three studies.
c The maximum score (-1 to +3) for each patient among the four doses summarized for the control group in studies BR1-019A and -019B.
Source: Sponsor's table Q (Studies BR1-019A, BR1-019B, and BR1-013 clinical trial reports).

3.2.4.3 Statistical Review of the Submission in 2001 (Dr. A. Mucci)

Dr. A. Mucci provided statistical review of the submission in 2001. This submission and the current submission have the same data. Reader is referred to his review documented in darrts which includes several secondary efficacy objectives. Dr. Mucci also investigated several alternative global measures for LVEBD and determined that these alternative global measures for LVEBD were just as bad as proposed method of partitioning LVEB into 12 viewable segments resulting into LVEBD ranging from 0 to 24 in correlating positively with LVEF Accuracy.

He performed several exploratory analyses. Some of the analyses related to segment by segment analyses are given in the Tables 9 to 11.

Reference ID: 3189315

Table 9: Comparison of Pre (Baseline) vs Post (Sonovue Enhanced) LVEBD Scores
Restriction is to Worse/Same/Better overall LVEBD Score. All Available Reads at 1mL and 2mL
Baseline reads are restricted to Suboptimals LVEBD<=14 in all Studies

Study Readers	N	PostScore< PreScore (Worse)	PostScore= PreScore (Same)	PostScore> PreScore (Better)
BR1-019A				
Reader#1	152	2%	5%	93%
Reader#2	152	8%	6%	86%
BR1-019B				
Reader#1	103	6%	9%	85%
Reader#2	96	0%	2%	98%
BR1-013				
Reader #1	106	5%	27%	68%
Reader#2	106	8%	5%	87%

Table 10: Percent of Suboptimal Baseline Reads for which Enhanced Reads are Adequate
All Blinded Readers - Doses 1mL and 2mL

STUDY	Y = #Suboptimal Pre-Dose Reads	X = #Adequate Post-Dose Reads among the Suboptimal Pre-Dose Reads	% Improvement =X/Y
BR1-019A	275	145	53%
BR1-019B	188	122	65%
BR1-013	187	46	25%

Suboptimal means LVEBD<=14; Adequate means LVEBD>14

Table 11: Segment by Segment Comparison of Dose vs. Baseline Suboptimal Reads for LVEBD
All Readers All Apical Segments Doses 1mL and 2mL. All Baseline reads were Suboptimal

STUDY	N (# segment reads)	DoseScore < BaseScore	DoseScore = BaseScore	DoseScore > BaseScore
BR1-019A	3432	2%	44%	54%
BR1-019B	2658	2%	37%	61%
BR1-013	2316	4%	57%	39%

The endpoint of overall apical LVEBD improves, both cumulatively over all segments, and also over individual segments, for Sonovue images in comparison to suboptimal baseline images.

3.3 Evaluation of Safety

The incidence of serious reactions was very low (3 cases, 0.1%); in all cases, the relationship with SonoVue could not be reasonably ruled out. For detailed safety review, the reader is referred to clinical review report.

Reference ID: 3189315

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

For the purposes of comparison within subgroups, data were combined for the total LV endocardial border delineation score (preinjection, postinjection, and change from baseline) and number of segments with adequate border delineation for the 3 confirmatory studies. Due to differences in design between the BR1-019A/-019B and BR1-013 studies, no statistical testing of these pooled data was performed. The primary endpoint is an ordinal discrete random variable. Normal approximation to the mean change from the baseline was used to compute 95% confidence interval for mean change from baseline.

When change from baseline in endocardial border delineation score was analyzed by gender and race, there appears to be similar effect reflected by an overlap in the 95% confidence intervals (CI) for the mean change from baseline at all SonoVue doses (Tables 12 and 13). The 95% confidence intervals (CI) for mean change from baseline overlapped for all three weight groups (<75, 75-100, >100 kg) also overlapped. There were no other apparent trends related to demographic or baseline characteristics including gender, presence of a pulmonary disorder, NYHA Class, or ejection fraction

Table 12: Analysis by Gender

Change From Baseline in Total LV Endocardial Border Delineation Score (BR1-019A, BR1-019B, BR1-013), Off-site Image Evaluation, Subset by Gender Group

Study Agent	Dose	N[a]	Mean Baseline (Preinjection)	Mean Change from Baseline	95% CI for Mean Change from Baseline[b]
Gender: Male SonoVue	0.5 mL	89	6.3	7.6	6.55, 8.69
	1.0 mL	127	7.7	6.7	5.85, 7.49
	2.0 mL	127	7.4	8.0	7.17, 8.87
	4.0 mL	89	6.4	10.0	8.97, 10.96
Gender: Female SonoVue	0.5 mL	49	7.8	7.4	6.11, 8.69
	1.0 mL	64	8.3	8.0	6.91, 9.04
	2.0 mL	64	8.5	8.1	6.99, 9.19
	4.0 mL	49	8.0	10.3	9.30, 11.33

Total score is the sum of scores of the apical 4-chamber and apical 2-chamber view.
Each view consists of six segments. Scores for each segment are as follows:
Score: 0 = Inadequate (border not visible);
+1 = Sufficient (border barely visible);
+2 = Good (border clearly visible).
Off-site reader assessments (Reader A and Reader B) were averaged for each patient at each dose.
a Includes patients who had both preinjection and postinjection image evaluations at each dose.
b 95% confidence interval (CI) for the mean change from baseline using the variability (SE) of the change from baseline.

Reference ID: 3189315

Table 13: Analysis by Race

Change From Baseline in Total LV Endocardial Border Delineation Score (BR1-019A, BR1-019B, BR1-013), Off-site Image Evaluation, Subset by Race Group

Study Agent	Dose	N[a]	Mean Baseline (Preinjection)	Mean Change from Baseline	95% CI for Mean Change from Baseline[b]
Race : White SonoVue	0.5 mL	112	6.7	7.4	6.46, 8.34
	1.0 mL	151	7.9	6.7	6.01, 7.47
	2.0 mL	151	7.6	7.9	7.09, 8.61
	4.0 mL	112	6.8	9.9	9.06, 10.67
Race : Non-white SonoVue	0.5 mL	26	7.5	8.2	6.43, 9.88
	1.0 mL	40	7.9	8.5	7.07, 9.91
	2.0 mL	40	8.6	8.8	7.31, 10.22
	4.0 mL	26	7.9	11.1	9.34, 12.77

Off-site reader assessments (Reader A and Reader B) were averaged for each patient at each dose.
a Includes patients who had both preinjection and postinjection image evaluations at each dose.
b 95% confidence interval (CI) for the mean change from baseline using the variability (SE) of the change from baseline.

Analysis by Age

When change from baseline in endocardial border delineation score was analyzed by age (Table 14), there was an indication of an effect on the response to SonoVue. As shown in Table 14, at each of the four dose levels of SonoVue, the mean change from baseline in endocardial border delineation score was lower for patients ≥ 65 years of age compared with those less than 65 years of age. For the three lower SonoVue doses (0.5, 1, and 2 mL), there was little to no overlap of the 95% confidence intervals (CI) for the mean change from baseline for the two age subgroups, suggesting a difference in response between the two age groups. At the 4- mL SonoVue dose, the difference between subgroups was less marked.

Table 14: Analysis by Age

Change From Baseline in Total LV Endocardial Border Delineation Score (BR1-019A, BR1-019B, BR1-013), Off-site Image Evaluation, Subset by Age Group

Study Agent	Dose	N[a]	Mean Baseline (Preinjection)	Mean Change from Baseline	95% CI for Mean Change from Baseline[b]
Age: 18-64 yrs SonoVue	0.5 mL	92	7.0	8.3	7.35, 9.35
	1.0 mL	118	7.9	7.8	7.02. 8.59
	2.0 mL	118	7.7	8.9	8.10, 9.68
	4.0 mL	92	7.3	10.4	9.48, 11.28
Age: ≥65 yrs SonoVue	0.5 mL	46	6.5	5.9	4.58, 7.29
	1.0 mL	73	7.9	6.0	4.88, 7.10
	2.0 mL	73	8.0	6.7	5.52, 7.82
	4.0 mL	46	6.4	9.5	8.25, 10.77

Off-site reader assessments (Reader A and Reader B) were averaged for each patient at each dose.
a Includes patients who had both preinjection and postinjection image evaluations at each dose.
b 95% confidence interval (CI) for the mean change from baseline using the variability (SE) of the change from baseline.

Reference ID: 3189315

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A previous NDA (# 21-315) was submitted to the FDA on January 21, 2001 in support of a similar indication for use in visualization of the endocardial border. (b) (4) The NDA was withdrawn by the sponsor on December 20, 2007. The sponsor was invited to present SonoVue US safety data to CRDAC in 2008. A meeting was held with DMIP to explore re-submission in 2009. In this meeting it was agreed that the primary database could rely on 3 prior confirmatory studies.

Sponsor submitted an original NDA with focus on agreed upon indication with FDA. There were no new data in this submission. The data submitted in 2001 were submitted again. These data were analyzed by Dr. Anthony Mucci and his report is available in darrts. The focus of this review is limited to the agreed upon indication and three pivotal studies.

The proposed indication is "SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification (LVO) and improve endocardial border delineation (EBD). Three adequate and well-controlled studies (BR1-019A, BR1-019B, and BR1-013) were identified and formed the basis for the evaluation of efficacy of SonoVue for EBD and LVO. These studies were single blind (subject blinded to identity and dose of agents administered), parallel-group comparisons of SonoVue and Albunex. Preinjection and postinjection echocardiographic images for each patient were evaluated by two off-site blinded, independent echocardiographers unaffiliated with any of the investigational sites of the study. All blinded reads followed a prospectively designed blinded read methodology.

Mean baseline (preinjection) and mean change from baseline for total left ventricular border delineation score are summarized in Table 15 for the 3 confirmatory studies.

Reference ID: 3189315

Table 15: Endocardial border delineation score

	Study BR1-019A			Study BR1-019B			Study BR1-013		
Reader A*	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change	N**	Mean Baseline	Mean Change
Dose SonaVue(mL)									
0.5	75	7.2	4.6	62	8.9	3.8		--	--
1.0	76	7.9	4.7	62	8.9	3.9	53	12.0	4.6
2.0	76	7.5	7.0	62	9.0	5.1	53	11.9	3.6
4.0	75	7.5	7.1	62	8.7	5.0		--	--
Reader B*									
Dose SonaVue(mL)									
0.5	76	6.7	8.8	62	4.6	13.4	--	--	--
1.0	76	8.0	8.8	61	4.6	16.2	53	6.3	4.1
2.0	76	7.6	9.6	62	4.6	17.2	53	6.7	4.5
4.0	76	7.2	10.7	62	4.2	18.2	--	--	--

* Different readers in each of the three studies.

** # of patients who had both the pre- and postinjection image evaluation at each dose

Left Ventricle Opacification (LVO) Scores is defined as:

-1 Non-Diagnostic Images
0 None (no visible contrast)
1 Faint (weak or trace effect of contrast within left ventricle0
+2 moderate (some areas of the left ventricle fully opacified but without a time when whole cavity is filled with contrast of the same high intensity)
+3 complete (homogeneous, high intensity contrast effect)

Across all off-site readers, opacification scores of +2 or +3 were recorded for more than 70% of patients in all SonoVue dose groups, and more than 85% of patients in the 2-mL and 4-mL dose groups.

5.2 Conclusions and Recommendations

In general, the Sponsor's results demonstrated significant improvement in Sonovue LVEBD over baseline LVEBD in all the submitted studies, with roughly similar levels of improvement across the studies. Moreover, additional investigations of suboptimal versus optimal images provided further favorable evidence of such improvement, as did the segmental level visibility comparisons. Dr. A. Mucci and this reviewer's analyses provide adequate evidence to support the proposed indication for SonoVue.

Reference ID: 3189315

SIGNATURES/DISTRIBUTION LIST

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Date: July 20 , 2012

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File: C:\CDER\2012 IND NDA\NDA 203-684 Review Stat SonoVue Rev 6 Sept 2012.doc

Reference ID: 3189315

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/s/

SATISH C MISRA
09/14/2012

JYOTI ZALKIKAR
09/14/2012
I concur with the primary reviewer.

THOMAS E GWISE
09/17/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA 203-684 Supp 00 Statistics Filing Memo

NDA Number: 203-684 Supp 00 **Applicant:** Bracco Diagnostics Inc. **Stamp Date:** 12-21-2011

Drug Name: SonoVue™ (Sulfur Hexafluoride) Microbubbles Injection **NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials –
The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
BR1-019A	parallel-group design with patient serving as their own control	SonoVue group (n=76) Vs control group (n=76) (Saline or Albunex)	Mean increase from baseline for the SonoVue group Total LV Endocardial Border Delineation Score as compared to the control group (Saline or Albunex)	statistically greater for SonoVue group when compared to the control group
BR1-019B	parallel-group design with patient serving as their own control	SonoVue group (n=62) Vs control group (n=62) (Saline or Albunex)	Mean increase from baseline for the SonoVue group Total LV Endocardial Border Delineation Score as compared to the control group (Saline or Albunex)	statistically greater for SonoVue group when compared to the control group
BR1-013	Cross-over design	SonoVue group (n=53) Vs control group (n=53) (Albunex)	Mean increase from baseline for the SonoVue group in total LV EBD Score as compared to the control group (Saline or Albunex)	statistically greater for SonoVue group when compared to the control group

Comments: This NDA was done in 1997. [redacted] (b) (4) Datasets for the three Confirmatory studies, the ISS and the ISE are submitted. The define.pdf for each of the studies is included.

Satish C. Misra, Ph. D. March 7, 2012
Reviewing Statistician Date

Jyoti Zalkikar, Ph. D. March 7, 2012
Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

SATISH C MISRA
03/07/2012

JYOTI ZALKIKAR
03/08/2012

Statistical Review and Evaluation
Clinical Studies

NDA#21315

Drug: Sonovue (SF_6)

Category: Microbubble Ultrasound Contrast Agent

Indication: Visualization of Cardiac Chambers [redacted] (b) (4)

Document Date: January 29 2001

PDUFA Goal Date: November 29 2001

Medical Officer: Nelson Arnstein, M.D.

Statistical Reviewer: A G Mucci, Ph.D.

Key Words: Clinical Studies, NDA Review, Diagnostic Trials

Sponsor's Proposed Indications:

(1): *Endocardial Border Delineation*
Sonovue can be used in Echocardiography in patients [redacted] (b) (4) to improve Visualization of cardiac chambers and Endocardial Border Delineation. [redacted] (b) (4).

[redacted] (b) (4)

Preliminary Comment

NDA21315 consists of results from a large number of clinical trials which can be broadly partitioned into two classes:

(A): Cardiovascular Trials: BR1-011 ; BR1-012 ; BR1-013 ; BR1-019A ; BR1-019B

(b) (4)

This statistical review will address these two classes of trials separately, with the cardiovascular trials review preceding the (b) (4), which begins on page 19. The cardiovascular trials review is the content of Section (1) below. The statistical cardiovascular review will essentially take the shape of an integrated analysis in which the principal results from the four trials, BR1-011, BR1-013, BR1-019A and BR1-019B will be compared and combined. The cardiovascular trials review will exclude BR1-012, since the design of this trial, which incorporated pharmacologic stress/rest testing, differed essentially from the design of the other cardiovascular trials, which focused on rest echo Imaging. For purposes of the analysis carried out in this review, and for both the cardiovascular trials (b) (4), only such description of the trial designs as is essential will be included. An overall summary of the results from the cardiovascular trials is presented on page (17); an overall summary of the results from the (b) (4) is presented on page (28).

Section(1): Cardiovascular Review

Overview of Results from the Cardiovascular Trials

The Primary Efficacy Endpoint for the Cardiovascular Trials was Left Ventricular Endocardial Border Delineation (LVEBD) which was measured, principally, as a sum of visibility scores over all the segments constituting the Apical border. This Endocardial Border score was assumed to be representative of an overall level of Apical Endocardial Border "visibility". (b) (4)

The Primary Efficacy Objective of the trials was to establish that Sonovue Enhanced Echocardiography provided significantly larger increases in LVEBD scores over Baseline scores than did the Active Control Albunex, and also to determine the optimally efficacious dose of Sonovue with respect to this LVEBD score increase over baseline. The FDA medical team advised the statistical reviewer that the active control Albunex is no longer used routinely for Echocardiography, therefore the emphasis of this statistical review with respect to the primary efficacy endpoint will be on direct comparisons of Sonovue Enhanced Echo LVEBD to Baseline Echo LVEBD, without mention of Albunex, and strictly to determine if Sonovue images provided greater LVEBD visibility than did baseline, and which dose level achieved the best such visibility differential.

In most of the trials under review the Baseline LVEBD was required to be Suboptimal (defined below in the description of Trials 19A/19B on page (7)), since the presumed rationale for Sonovue Echo, in practice, would be a suboptimal baseline Echo. Consequently, in addition to the relatively straightforward overall Sonovue vs Baseline LVEBD score comparisons, several alternative comparisons of Sonovue Echo vs Baseline Echo are also carried out in order to determine the likelihood that a suboptimal baseline Echo is transformed into an adequate or optimal Sonovue Echo. Further, a segment by segment visibility comparison, Sonovue vs Baseline, was carried out by the reviewer in order to more adequately understand the "local" effect of Sonovue on border visibility.

In general, the Sponsor's results demonstrated significant improvement in Sonovue LVEBD over baseline LVEBD in all the submitted studies, with roughly similar levels of improvement across the studies. Moreover, the reviewer's additional investigations of suboptimal vs optimal images provided further favorable evidence of such improvement, as did the segmental level visibility comparisons. However, in all these studies of Sonovue vs baseline LVEBD, no further improvements were evident for doses larger than 1mL.

Since the primary endpoint of LVEBD score is "soft", this review also focused considerable attention on several secondary efficacy objectives, which assessed levels of Agreement of Echo based WM Diagnoses and Echo based LVEF measurements with appropriate Truth Standards, wherever such standards were available. For instance, direct comparisons of LVEBD score levels with Agreement levels in WM Diagnoses and with LVEF Accuracy were investigated by the reviewer. Although, as stated above, the Sponsor's results demonstrated significant and similar improvement in LVEBD for Sonovue Enhanced Echo over Baseline Echo in all the studies under review, LVEF

Accuracy revealed little or no improvement for Enhanced Echo over Baseline Echo. Moreover, LVEF Accuracy presented no significant correlation with levels of LVEBD. That is, higher levels of LVEBD did not translate into increasingly accurate LVEF evaluations. However, in the one study in which WM was formally examined and reviewed, the Sponsor's results suggest that WM Diagnostic Accuracy improves from Baseline Echo to Sonovue Enhanced Echo, and that this improvement correlates directly with increased levels of LVEBD. This currently limited evidence (b) (4)

Remarks: Clinical Trials BR1-019A, BR1-019B and BR1-011 also included another Primary Efficacy Endpoint – Duration of Useful Contrast Effect. This endpoint is not discussed in this review since the medical review team does not consider it to be a meaningful diagnostic endpoint, and since it cannot be meaningfully compared to the baseline, where there is no duration of contrast. However, the Sponsor's principal results regarding this endpoint are included in the medical review.

Description of the Primary Efficacy Endpoint Score

All of the Cardiovascular trials designated Left Ventricular Endocardial Border Delineation (LVEBD) as a primary endpoint. The rationale for this emphasis is the a priori reasonable assumption that improved border visibility for Enhanced Images over Baseline Images should translate into improved accuracy for diagnostic endpoints such as Left Ventricular Ejection Fraction (LVEF) and Wall Motion (WM). However, there is no obvious path from the diagnostician's intuitive assessment of border visibility to a statistically suitable measure of such visibility. The Sponsor has chosen throughout to measure LVEBD in the manner defined directly below, which shall be here defined as:

Measure#1:

(a): The LVEB is partitioned into viewable segments: 12 Apical and (sometimes) 10 Parasternal segments.

(b): Each segment is scored as:

0 if inadequately delineated; 1 if sufficiently delineated ; 2 if well delineated.

(c): LVEBD is then defined as the sum over all the segments.

Thus:
Apical LVEBD ranges from 0 to 24
Parasternal LVEBD ranges from 0 to 20
Total LVEBD ranges from 0 to 44

This LVEBD score is consistent with LVEBD scores which have figured prominently in several recent clinical trials for other diagnostic imaging agents. This near universality in this choice of a "global" measure for LVEBD is, however, no guarantee that it mathematically captures the diagnostician's unquantified assessment of overall degree of border delineation. In fact, within the trials under review, as well as the other trials alluded to above, this measure for LVEBD did not correlate in any significant manner with LVEF Accuracy, so that if one wishes to maintain the hypothesis that improved LVEBD should translate into improved LVEF Accuracy, then the chosen measure for LVEBD presents little evidence of having captured the diagnostician's LVEBD assessment. WM diagnostic accuracy, however, appears to be somewhat more amenable to positive concordance with the Sponsor's LVEBD score.

In an attempt order to carry the LVEBD analyses further than would be possible with LVEBD as defined above, at least two other measures for "global" LVEBD were defined by and to some degree investigated by the Reviewer:

Measure#2:

(a): Score each Apical Segment as 0 = Not Delineated ; 1 = Delineated

(b): Set LVEBD = Sum of scores over all Apical segments (Score = 0 to 12)

Measure#3:

(a): Specify all pairs of contiguous segments (there are twenty of them.)

(b): Score each contiguous pair as: 0 if neither segment is delineated; 1 if at least one segment from the pair is delineated

(c): Set LVEBD = Sum of scores over all 20 pairs (Score = 0 to 20)

(The rationale behind this score is the assumption that non-visibility of contiguous segments could be more seriously implicated in inaccuracies in LVEF and WM diagnoses than non-visibility of isolated segments.)

The reviewer determined, on the basis of his own investigations, that neither of these alternative global measures for LVEBD was any more successful than Measure#1 in correlating positively with LVEF Accuracy. The analyses of these measures conducted by the reviewer will not be included in this report, and therefore LVEBD in this review will invariably be restricted to mean LVEBD as defined under Measure#1. Moreover, since Parasternal LVEBD showed no improvement, Enhanced Images over Baseline Images, LVEBD in this Review will invariably mean Apical LVEBD.

Description of the Efficacy Endpoint Investigations

This Statistical Review of the Cardiovascular trials will concentrate on investigations of the following three sets of endpoints:

(I): *Improvements in LVEBD for Sonovue Enhanced Echo Images over Baseline LVEBD*. The Sponsor has powered the trials at level .80 to detect a mean gain of at least 2 LVEBD units for Enhanced Images over Baseline Images. The LVEBD scores, restricted to Sonovue vs Baseline, will be analyzed from several points of view additional to the comparison of means so that the implications of LVEBD as defined in Measure#1 become somewhat more transparent. In particular, *Improvements of Enhanced Echo vs Baseline Echo* which focus on the segment by segment scores will also be investigated.

(II): *Enhanced Image LVEF Accuracies versus Baseline Image LVEF Accuracies*. These comparisons will be made through a comparison of Enhanced Echo LVEF to Baseline LVEF, without regard to LVEBD, and then, indirectly, through an analysis of concordances of LVEF Accuracies, regardless of Image type, with levels of LVEBD.

(III): *Enhanced Image WM Diagnosability vs Baseline Image WM Diagnosability*. These comparisons will be made both directly – WM Diagnosability with respect to the categories of Enhanced vs Unenhanced Images, - and indirectly - WM Diagnosability as a function of LVEBD levels. It will be shown that WM Diagnosability improves, in several senses, as LVEBD increases, and therefore favors Enhanced Images over Baseline Images. However, Diagnosability is itself a "soft" endpoint which ignores actual diagnoses, and since no Reference Modality was employed to corroborate the diagnoses, and since the study which evaluated WM was small (53 patients), these positive results, though suggestive, are far from conclusive.

The Statistical Analysis, based largely on Table(1) through Table(8) and Plot(1) through Plot(5) along with their accompanying comments, follows the synopses of the individual trials which are presented directly below.

Trials Synopses

Clinical Trial BR1-011:
Title: A Multicenter Study to evaluate the Safety and Efficacy of different doses of SONOVUE as an Ultrasound Contrast Enhancing Agent in adult patients undergoing Two Dimensional Transthoracic Echocardiography at Rest.

Synopsis: A European Phase II/III Crossover Dose-Ranging Study of 215 patients with suspected heart disease. Sonovue was administered at four doses (.5mL, 1mL. 2mL, and 4mL) in a randomized sequence in one imaging session. The Primary Efficacy Objectives were to determine the optimal dose for increase over baseline in Left

Ventricular Endocardial Border Delineation (LVEBD) and for Duration of Contrast. An important Secondary Efficacy Objective was the evaluation of the Accuracy of On–Site Baseline and Enhanced Echo LVEF through comparison with a Reference LVEF, which was based on Cardioangiography, Nuclear Cardioangiography, or Cardiac MRI. (136 of the 215 patients underwent such reference procedures.) The Off-Site reads of the images, which primarily yielded scores for the LVEBD and Contrast Duration endpoints, were carried out by two pairs of two independent blinded readers, with each pair reading approximately half the images. The primary endpoint of patient LVEBD was the sum of segmental delineation scores over 12 Apical segments and 10 Parasternal segments. The trial was powered at level .80 to detect an increase of at least 2 LVEBD units for Enhanced Images over Baseline Images. The LVEBD analysis below will be restricted to Apical LVEBD, and will concentrate on the 1mL and 2mL dose results.

Clinical Trial BR1-013:
Title: A Single-Blind Multicenter Randomized Crossover Study to Evaluate the Efficacy and Safety of SONOVUE Versus Albunex as a Contrast Enhancing Agent for Transthoracic Echocardiography at Rest.

Synopsis: USA Phase II/III Crossover Dose-Ranging and Active Control Study of 53 patients with suspected heart disease who presented with suboptimal Apical LVEBD on a routine echocardiogram, which was defined as a total LVEDB score of at most 14, but with a minimum of four segments with scores of at least 1. Patients received two doses of Sonovue (1mL and 2mL) and one dose of Albunex (.22mL/Kg) in a randomized sequence in one imaging session. The Primary Efficacy Objectives were to compare Sonovue to Albunex with respect to increases over baseline in LVEBD scores. An important Secondary Efficacy Objective was the evaluation of Accuracies of Off-site Sonovue and Albunex Enhanced Echo- based LVEF calculations with respect to a Reference LVEF. Another Secondary Efficacy Objective was the evaluation of improvement over Baseline for Wall Motion Diagnosability, Sonovue vs Albunex. (No Standard of Truth.) Two blinded readers independently read all Images. The Apical LVEBD scoring protocol was identical to that of BR1-011. Thus, the total possible LVEBD score ranged from 0 to 24 units. The LVEF calculation followed a complicated protocol, with one of the two blinded readers providing a tape segment from which a third reader calculated LVEF, and with a fourth reader brought into the study to independently recalculate LVEF once it was decided that the third reader's Baseline LVEF assessments presented too large a variance. (This final reader's LVEF assessments were not constrained by the tape segment selections imposed by the original reader.) The trial was powered at level .80 to detect a difference of 4 LVEBD units, Sonovue vs Albunex, in mean improvement of Enhanced Images over Baseline Images. Once more, within this Review, comparisons of Sonovue to Albunex will be ignored.

Clinical Trials BR1-019A and BR1-019B:
Title: A Multicenter Clinical Evaluation of the Safety and efficacy of SonoVue versus Albunex as a Contrast Enhancing Agent for Transthoracic Echocardiography at Rest.

Synopsis: USA Phase II/II combination Parallel Group and Crossover Dose Ranging studies of patients who were suspected for heart disease and who presented with suboptimal LVEBD (Apical LVEBD<=14) on a routine Echo. Patients were randomized into either a 4 dose (.5mL. 1mL, 2mL, and 4mL) Crossover Sonovue Arm, or into a 4 dose (.08ml/kg Albunex, .22mL/Kg Albunex, and two placebo doses) Crossover Albunex Arm. Study BR1-019A enlisted 76 patients for Sonovue and 67 patients for Albunex; Study BR1-019B enlisted 62 patients for Sonovue and 59 patients for Albunex. The Primary Efficacy Objective was the comparison of Sonovue to Albunex with respect to improvements, Enhanced Images over Baseline Images, in the total LVEBD score. As with BR1-013, these trials restricted LVEBD evaluations to Apical segments. Each Study provided two independent blinded readers. (There is a design complication: the blinded readers in each study were investigators in the other study.) The trials were powered at level .80 to detect a difference of 4 LVEBD units, Sonovue vs Albunex, in mean improvement of Enhanced Images over over Baseline Images. As stated above, this Review will bypass Sonovue vs Albunex comparisons.

The statistical analyses for these trials are presented directly below. The conclusions drawn from these analyses follow Table(8).

Statistical Analyses

(I): *Analysis of Improvements in LVEBD Scores from Baseline Echo to Enhanced Echo*

TABLE (1)
Mean Total Apical LVEBD by Study/Reader/Dose
(Baseline reads are restricted to Suboptimals (LVEBD<=14))
Sponsor's LVEBD Endpoint

Study	Reader	Dose = 1mL			Dose = 2mL	
		Pre-Dose	Post-Dose Increase		Pre-Dose	Post-Dose Increase
BR1-011	1 (N=77)	8.4	1.7		8.4	1.6
	2 (N=33)	11.1	4.5		11.1	4.6
	3 (N=69)	8.8	6.3		8.8	6.5
	4 (N=34)	9.0	9.8		9.0	8.8
BR1-013	1 (N=53)	12.0	4.6		11.9	3.6
	2 (N=53)	6.3	4.1		6.7	4.5
BR1-019A	1 (N=76)	7.9	4.7		7.5	7.0
	2 (N=76)	8.0	8.8		7.6	9.6
BR1-019B	1 (N=62)	8.9	4.0		9.0	5.1
	2 (N=62)	4.6	16.2		4.6	17.3
Combined*		8.9	5.2		8.7	5.7

Notes/Comments:

N = Number of Subjects contributing at least one baseline and one dosed read. In BR1-011, Reader#1 and Reader#2 both read images for 99 subjects; Reader#3 and Reader#4 both read images for 116 other subjects. This study did not require a suboptimal baseline at screening, consequently there was a considerable reduction in patients admitted into the table above when reads were restricted to subjects with suboptimal baselines acquired during the trials. All other studies required a suboptimal unenhanced read at screening.

In BR1-013, Reader#1 and Reader#2 both read images for 53 subjects.

In BR1-019A, Reader#1 and Reader#2 both read images for 76 subjects.

In BR1-019B, Reader#1 and Reader#2 both read images for 62 subjects.

* The Combined entries are averages over all readers except Reader#2 from Study BR1-019B. (This reader's results were considered to be outliers.)

Conclusion from the Table: *Sonovue Enhanced Images provide a mean increase over baseline in Apical LVEBD scores of about 5 to 6 units when the Baseline is suboptimal.*

Important Remark: In all the tables and plots connected with the analyses which follow, data will be combined for 1mL and 2mL doses of Sonovue. The rationale behind this pooling of data is the similarity of LVEBD and LVEF Accuracy results at 1mL and 2mL as indicated above. Furthermore, the appendix provides a table which documents this similarity for LVEBD. *In light of this similarity this reviewer concludes that 2ml provides no additional efficacy over 1mL.*

We turn now to Dosed vs Baseline comparisons of overall LVEBD scores (Measure#1 above) as worse, same better.

TABLE(2)
Comparison of Pre (Baseline) vs Post (Sonovue Enhanced) LVEBD Scores
Restriction is to Worse/Same/Better overall LVEBD Score
All Available Reads at 1mL and 2mL
Baseline reads are restricted to Suboptimals in all Studies

	N	PostScore<PreScore (Worse)	PostScore=PreScore (Same)	PostScore>PreScore (Better)
BR1-011				
Reader#1	137	34%	8%	58%
Reader#2	131	12%	5%	83%
Reader#3	271	17%	3%	80%
Reader#4	110	9%	5%	86%
BR1-013				
Reader#1	106	5%	27%	68%
Reader#2	106	8%	5%	87%
BR1-019A				
Reader#1	152	2%	5%	93%
Reader#2	152	8%	6%	86%
BR1-019B				
Reader#1	103	6%	9%	85%
Reader#2	96	0%	2%	98%
Combined*		12%	7%	81%

Notes/Comments:

N = Number of Reads (Should be approximately twice the number of Subjects, except for BR1-011, where a considerable number of subjects were excluded by the Reviewer for purposes of restriction of the analysis to subjects with suboptimal baseline. (All other studies were restricted to patients with suboptimal Baseline LVEBD by virtue of their Inclusion Criteria.)

Note: Combined* once more excludes Reader#2 from BR1-019B

Conclusion: *Total mean Apical LVEBD for Enhanced Images represents a considerable improvement over Baseline LVEBD when the measure is Worse/Same/Better. However, this improvement does not reflect segment by segment based performance, which will be presented later, statring with Table(5).*

The next comparison of Baseline vs Sonovue reads concentrates on the extent to which suboptimal baselines improve to optimal Sonovue images. Once more, the measure utilized is the Sponsor's Measure#1.

TABLE(3)
Percent of Suboptimal Baseline Reads for which Enhanced Reads are Adequate
All Blinded Readers Doses 1mL and 2mL

STUDY	Y = #Suboptimal Pre-Dose Reads	X = #Adequate Post-Dose Reads among the Suboptimal Pre-Dose Reads	% Improvement=X/Y
BR1-011	395	193	49%
BR1-013	187	46	25%
BR1-019A	275	145	53%
BR1-019B*	94	40	43%
BR1-019B	188	122	65%
Combined*	951	424	45%

Comments

Suboptimal means LVEBD<=14; Adequate means LVEBD>14 (Sponsor's definition of suboptimal, reviewer's definition of adequate, since the sponsor supplied no definition for LVEBD>14)

BR1-019B* is again restricted to Reader#1; Combined* is the average over BR1-011, BR1-013, BR1-019A and BR1-019B*.

Conclusion: *A suboptimal baseline LVEBD Read will become an adequate enhanced read in approximately one in every two cases. (This is not an especially powerful result.)*

Another way to evaluate Baseline vs Sonovue LVEBD global score is to examine the mean increases in Sonovue scores for various levels of baseline scores. This statistic is exhibited in the table below.

TABLE(4)
Ranges of Mean LVEBD Improvement for Enhanced Images Over Baseline Images
All Studies All Readers Doses 1mL and 2mL
All baseline reads are suboptimal (LVEBD<=14)

Baseline LVEBD	N	Range of Dosed LVEBD	Range of Mean LVEBD Improvement Over Baseline
0<= B<=2	79	5<=D<=8	5<=D<=7
3<=B<=10	549	11<=D<=14	4<=D<=8
11<=B<=14	319	17<=D<=19	4<=D<=6

N = # Reads = 947

Comments: The Table is to be read as follows:

For the spread of individual Baseline LVEBD scores in the range 3 to 10, the Mean Dosed LVEBD ranges from 11 to 14 and the Mean dosed change in LVEBD ranges from 4 to 8.

Conclusion: *Dosed Images remain, on the average, suboptimal for LVEBD when the Baseline Image LVEBD score ≤ 10. That is, the expected Dosed Image LVEBD score becomes, on the average, Adequate, only when the Baseline is, itself, close to adequate. Moreover, the Mean Improvement, Dosed Image over Baseline, is between 4 and 8 units for all Suboptimal Baseline values (0 through 14).*

Next, we turn to the segment by segment analyses. In these analyses the scores on individual segments are compared. The tables below were derived from raw data by the reviewer.

TABLE(5)
Segment by Segment Comparison of Dose vs Baseline Suboptimal Reads for LVEBD
All Readers All Apical Segments Doses 1mL and 2mL
All Baseline reads were Suboptimal

STUDY	N	DoseScore<BaseScore	DoseScore=BaseScore	DoseScore>BaseScore
BR1-011	4602	11%	48%	41%
BR1-013	2316	4%	57%	39%
BR1-019A	3432	2%	44%	54%
BR1-019B*	1356	2%	63%	35%
BR1-019B	2658	2%	37%	61%
Combined*	11208	6%	50%	44%

Notes/Comments:

N = Number of segment reads

Once more * indicates results exclusive of Reader#2 from BR1-019B.

Conclusion: On the average, on a segment by segment level, Dose LVEBD > Base LVEBD in slightly less than half of all segments. Moreover, in approximately half of all segments Dose LVEBD = Base LVEBD

(II*): Analysis of Baseline LVEF vs Enhanced LVEF Accuracies and their relation, or lack thereof, to Apical LVEBD.*

The evidence adduced from the tables above as indicative of Sonovue Efficacy with respect to the "soft" endpoint of global or segmental LVEBD does not, in itself, ensure that Sonovue Echo will improve over Baseline Echo with respect to functional endpoints. In particular, although Sonovue Images provide larger LVEBD scores, the two plots which follow directly below reveal that Sonovue Echo LVEF Accuracies do not significantly improve over Baseline Echo LVEF Accuracies. Two regression plots, presented in Appendix(1), reveal that the spread of calibrated Sonovue Echo LVEF values around Reference RVG LVEF values are not significantly tighter than the spread of Baseline Echo LVEF values around Reference RVG LVEF values. The Sonovue Echo images used for the LVEF calculation come from the 4mL dose since this dose presented the most favorable correlations and residuals.

The essential statistics are:

Baseline vs Reference Correlation = .77 ; Residual of Baseline around Reference = 13.2

Sonovue vs Reference Correlation = .86 ; Residual of Sonovue about Reference = 9.6

Thus, the 4mL Sonovue Echo LVEF is slightly more accurate than Baseline Echo LVEF, but this small gain in LVEF accuracy does not appear to be clinically significant.

Note:
A similar analysis was also carried out for the only other Study which included LVEF measurements, namely Study BR1-013. This latter Study included Off-Site LVEF measurements, which could, theoretically, provide a more objective means of assessing the Accuracy of Sonovue Image based LVEF. However, several complications arose in the Study which would temper positive interpretations of Sonovue LVEF Accuracy, even were strong levels of such accuracy discovered. Specifically, the Sponsor reported unacceptable levels of variation in the original off-site LVEF measurements derived from the baseline echo images. (These measurements were carried out by a third reader who calculated LVEF on the basis of tape segments determined by one of the blinded readers who scored LVEBD.) Consequent to this unacceptable result, a new, independent

sonographer was enlisted to recalculate LVEF, and it was the latter reader's LVEF measurements which were deemed most appropriate for comparison with reference LVEF. The problem here is that this new reader did not adjust his reads to directives provided by the initial blinded echo reader; specifically, he did not necessarily utilize those tape segments which that reader indicated as appropriate for LVEF calculations. This relaxation of the constraint imposed by the original blinded reader makes it difficult to directly correlate LVEBD with LVEF Accuracy, since the tape segments originally determined as appropriate for LVEF measurements, which presumably were influenced by that reader's perception of LVEBD, need not be the tape segments actually employed by the new reader for this purpose. This concern, however, is somewhat academic, since Sonovue based LVEF Accuracy was not especially superior to baseline LVEF Accuracy. The plots (A1 through A4) and results are presented in Appendix(1).

Comparisons of LVEF Accuracies to LVEBD Scores

Since Enhanced Echo LVEF is not significantly more accurate than Baseline Echo LVEF, while Enhanced LVEBD is significantly greater than Baseline LVEBD, it would appear unlikely that LVEF Accuracy improves as LVEBD improves. This assumption is borne out by the EF Accuracy vs LVEBD Scores Plot(A5) displayed in Appendix(1). The conclusion to be drawn from the plot is that there is no correlation between LVEF Accuracy and LVEBD scores. In the indicated plot Baseline and Enhanced Images are lumped together since the concern here lies solely with correlations between LVEBD levels and LVEF Accuracy. The data is restricted to BR1-013 since the LVEBD reads for that Study were blinded. (BR1-011 reveals a similar scatter.)

(III): *Wall Motion Analyses*

Wall Motion Analyses in this Review are restricted to BR1-013 since this was the onlt trial with a standard of truth to which WM reads could be compared. In Table(6) below Baseline Images are compared to Enhanced Images with respect to the category of WM Diagnosability, which is a reader determined soft endpoint that omits specification of the particulars of the diagnosis. As such, it should be expected to be correlated with LVEBD since adequate wall visibility would seem to provide adequate visibility of the character of Wall Motion. The concordances between LVEBD (Baseline or Enhanced) and WM Diagnosability are presented in Table(7). An image was defined by the Sponsor as normal, abnormal, or uncertain. The reviewer classified normals and abnormals as diagnosable; uncertains as non-diagnosable.

TABLE(6)
Comparisons for Patient Level Wall Motion Diagnosability
PreDose Images vs PostDose Images
Study BR1-013
All Blinded Readers Doses 1mL and 2mL Combined
Number of Patients = 53 Number of Reads = 212

Pre Dose	PostDose	
	Non-Diagnosable	Diagnosable
Non-Diagnosable	8 (4%)	23 (11%)
Diagnosable	1 (0%)	180 (85%)

Note that Diagnosable Images increase from 85% at Baseline to 96% at Enhancement. Moreover, 74% of the Baseline Non-Diagnosable Images become Diagnosable under Sonovue Enhancement. Of course, it must be stressed here that in this Study Diagnosability has no reference standard against which its truth was evaluated.

The next table measures diagnosability as a function of LVEBD levels, independently of the source image (baseline or dosed):

TABLE (7)
WM Diagnosability as a Function of LVEBD Scores
Study BR1-013
All Blinded Readers Doses 1mL, 2mL, and Baseline Combined
Number of Patients = 53 Number of Reads = 424

	WM Non-Diagnosable (N = 40)	WM Diagnosable (N = 384)
LVEBD < =14 (Suboptimal Score)	40	291
LVEBD is >14 (Adequate Score)	0	93

Note that:

Percent of Diagnosable WM's for Inadequate LVEBD's is 88%

Percent of Diagnosable WM's for Adequate LVEBD's is 100%

Further (Although not derivable from the tables above):

Mean LVEBD over Non-Diagnosable WM's = 2.8

Mean LVEBD over Diagnosable WM's = 12.2

Again, these statistics reveal that LVEBD scores and WM Diagnosability levels move in the same direction.

Another approach to assessment of Baseline vs Enhanced WM Diagnosability (in the absence of a Reference Standard) is the comparison, Baseline Images vs Enhanced Images, of Reader Agreement over the three WM categories: Non-Diagnosable, Normal, Abnormal.

TABLE(8)
WALL MOTION AGREEMENT TABLES
BR1-013
Readers treated Independently as Reader#1 = R1 and Reader#2 = R2
Number of Patients=53 Number of Baseline Reads = Number of Enhanced Reads = 106

	BASELINE				ENHANCED		
	R2=0	R2=Normal	R2=Abnormal		R2 = 0	R2 = Normal	R2 = Abnormal
R1 = 0	2	0	0		2	0	0
R1 =Normal	13	17	14		3	30	17
R1 =Abnormal	14	2	44		2	5	47

Note: R1=0 means R1=Non-Diagnosable; R2=0 means R2=Non-Diagnosable

Comments:
Agreement Level on WM Diagnosis at Baseline = 59%

Agreement Level on WM Diagnosis under Enhancement = 75%

Although not spectacular, or in any way definitive, this improvement in Reader Agreement from Baseline Images to Enhanced Images, provides some evidence that Enhanced Images could lead to improved precision in WM Diagnosability.

Summary and Conclusions on the Cardiovascular Trials

The four cardiovascular trials under review all defined LVEBD as their primary efficacy endpoint. LVEBD, in all cases, was measured and primarily analyzed as a sum of apical segmental scores, and the primary objective was to demonstrate that mean apical LVEBD scores improved significantly from baseline rest echo to Sonovue dosed rest echo. Dose ranging analyses were conducted coincident with this baseline versus enhanced image analysis.

In most of the trials under review the Sponsor required that the baseline image, at screening, be suboptimal. Suboptimal was defined, essentially, as a total apical LVEBD score of at most 14 (out of a possible 24). The statistical analysis conducted in this review therefore concentrated on data for which the baseline reads during the trials were suboptimal since it was assumed that the target population of patients for Sonovue rest echo imaging will be patients whose LVEBD at baseline is inadequate. The results demonstrated that 1mL Sonovue images provided significantly improved LVEBD scores over baseline images, and that higher doses did not significantly extend this improvement. On the average, Sonovue LVEBD increased by 5 units over baseline.

The reviewer extended this analysis (of mean baseline LVEBD scores versus mean Sonovue enhanced LVEBD scores) to subcategories of suboptimal baseline scores – baseline LVEBD at most 10 (out of a possible 14), for instance. It was found that mean enhanced LVEBD, when baseline LVEBD was at most 10, was at most 14. In effect, if the baseline was strongly suboptimal, the enhanced image remained, on the average, suboptimal. Another way of viewing this result is: The overall mean gain of 5 units in LVEBD from baseline to enhanced image was fairly consistent over various levels of baseline LVEBD, consequently very poorly visible baseline images (score at most 10) did not, on the average, become highly visible under Sonovue enhancement (score above 14).

In order to better understand the import of the global improvement in LVEBD, the reviewer examined LVEBD on a segment by segment basis, using the segment level categories: 'inadequately visualized' and 'adequately visualized'. The results demonstrated that approximately half of all segments inadequately visualized at baseline were adequately visualized under Sonovue enhancement.

The improvements in LVEBD were next examined with respect to their possible influence on efficacy of functional endpoints such as Wall Motion and LVEF. There was some limited evidence that Sonovue enhanced images provided improved WM diagnosability over baseline images, and that this improvement was correlated with higher LVEBD scores. The category of diagnosability is fairly soft, however, consisting of blinded reader judgments that the WM was classifiable as either normal or abnormal, while non-diagnosability represented the reader's inability to conclude on either such classification. Further, there was no standard of truth against which these judgments were evaluated, and the trial in which WM was analyzed contained only 53 patients.

There was very little improvement in LVEF accuracy for Sonovue images over baseline images. Accuracy, in this context, was measured through correlations of image scores with RVG scores, calculated first over the class of baseline images and then over the class of enhanced images. Further, there was no correlation between LVEF accuracy and LVEBD scores, regardless of the source (baseline or enhanced image) of the scores. Accuracy, in this instance, was measured by the absolute difference between echo based LVEF and RVG based LVEF. (The expectation, if LVEBD improvements were instrumental in LVEF assessments, would be that the difference between echo based LVEF and RVG LVEF would decrease as LVEBD scores increased.)

The overall conclusion to be drawn from these results is that the soft endpoint of overall apical LVEBD improves, both cumulatively over all segments, and also over individual segments, for Sonovue images in comparison to suboptimal baseline images, but these improvements are not reflected in improved LVEF accuracies, and are at best suggestive of improvements in WM diagnostic accuracy. A statistically and clinically realistic assessment of the relevance of LVEBD to WM Accuracy would require standard of truth WM diagnoses.

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A G Mucci, Ph. D.
Statistical Reviewer

Concur:

Michael Welch, Ph.D.

cc: Archival NDA#21315
HFD-160/A Loewke/N Arnstein
HFD-160/J Moore
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Appendix(1) Cardiovascular

TABLE (A1)
Segment by Segment Comparison of 1mL to 2mL LVEBD Diagnostics
(Readers combined in each Study)

STUDY	DOSE	Sample Size	Worse	Same	Better
BR1-011	1mL	2334	11%	49%	40%
	2mL	2268	12%	47%	41%
BR1-013	1mL	1182	4%	57%	39%
	2mL	1134	5%	57%	38%
BR1-019A	1mL	1686	2%	49%	49%
	2mL	1746	1%	40%	59%
BR1-019B*	1mL	696	3%	66%	31%
	2mL	660	1%	60%	39%
Combined*	1mL	5898	6%	53%	41%
	2mL	5808	6%	48%	46%
BR1-019B (R2)	1mL	672	0%	15%	85%
	2mL	630	0%	11%	89%

Notes/Comments

(1): “Worse” means Baseline Score> Enhanced score (Segment Level)

(2): “Same” means Baseline Score = Enhanced Score (Segment Level)

(3): “Better” means Baseline Score < Enhanced Score (Segment Level)

BR1-019B* is restricted to Reader#1

Combined* includes all readers except Reader#2 for BR1-019B

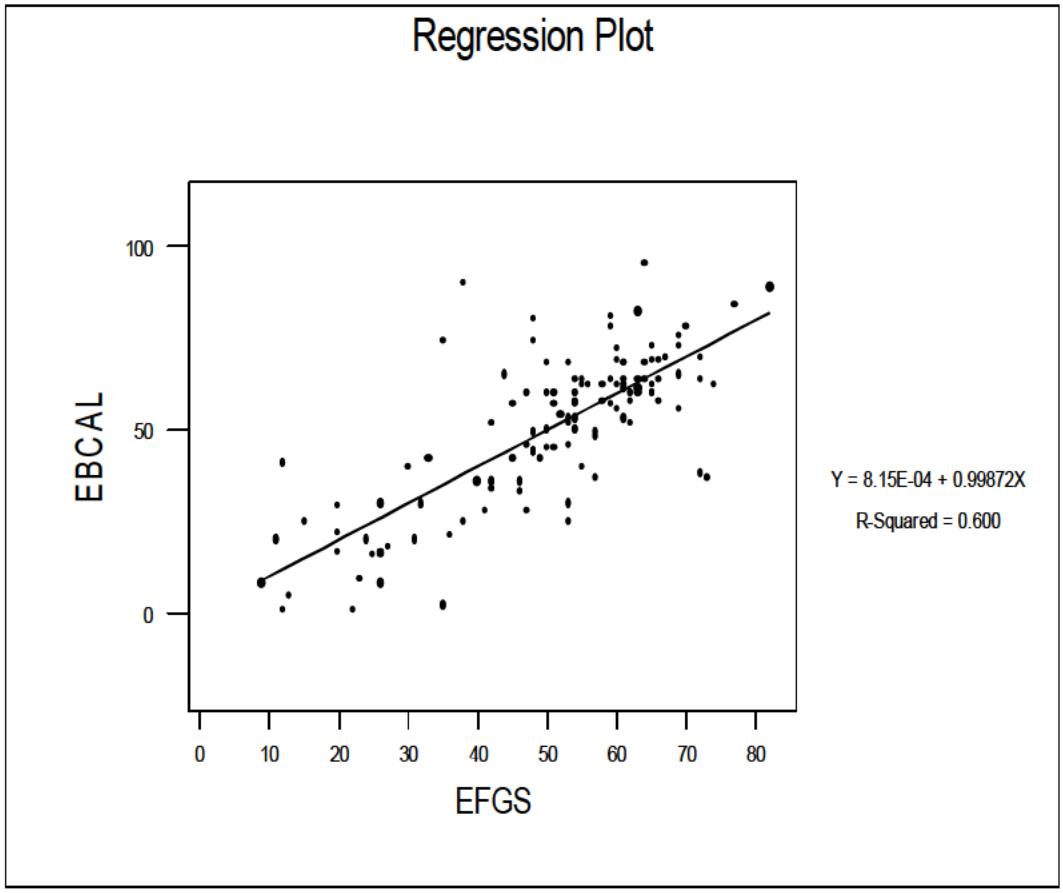
BR10019B (R2) presents results for Reader#2 for BR1-019B

Conclusions

(a): The 1mL and 2ml results are essentially the same across all studies

(b): Reader#2 for Study BR1-019B is an “Outlier”

Plot(A1)
Regression between *Calibrated Baseline* Echo LVEF and *Reference* LVEF
(Source is On-Site Data from Study BR1-011)
(Data consists of On-Site LVEF measurements on 126 patients)



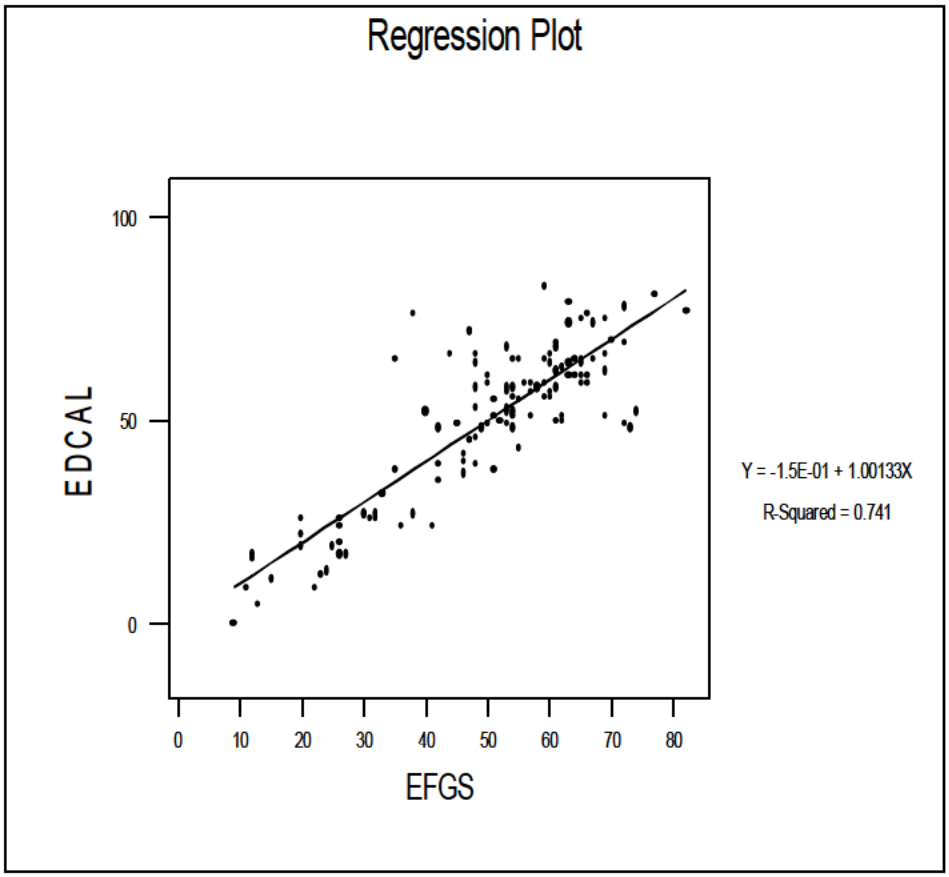
Comments:

(1): EFGS= Reference LVEF

(2): EBCAL = Linear Transform of Baseline Echo LVEF which best calibrates with Reference LVEF. (That is, to avoid differences in Echo LVEF and Reference LVEF which are simply matters of scale and shift factors, Baseline Echo LVEF was first transformed so as to match up with Reference LVEF except for scatter around the 45 degree line.) Thus, the fit displayed in the plot above is:

EBCAL = EFGS + Noise *with Correlation R = .77*

Plot(A2)
Regression between *Calibrated 4mL* Enhanced Echo LVEF and *Reference* LVEF
(Source is On-Site Data from Study BR1-011)
(Data consists of LVEF measurements on 126 patients)



Comments:

(1): EFGS= Reference LVEF

(2): EDCAL = Linear Transform of Dose 4mL Echo LVEF which best calibrates with Reference LVEF (That is, to avoid differences in Echo LVEF and Reference LVEF which are simply matters of scale and shift factors, 4mL Enhanced Echo LVEF was first transformed so as to match up with Reference LVEF except for scatter around the 45 degree line.) The 4mL Dose Echo LVEF was chosen because it yielded, marginally), the largest Correlation. Thus, the fit is:

EDCAL = EFGS + Noise *with Correlation R = .86*

Remarks: *It is not clear that the improvement in Correlation from a Baseline Echo LVEF vs Reference LVEF of .77 to an Enhanced Echo LVEF vs Reference LVEF of .86 represents either a significant Clinical or a significant Statistical improvement.*

In addition to Correlations, differences in LVEF (Reference LVEF - Image LVEF) were also enlisted by the Reviewer as gauges of Accuracy for Study BR1-011. In particular, mean differences and their precisions (Sigmas) were calculated.

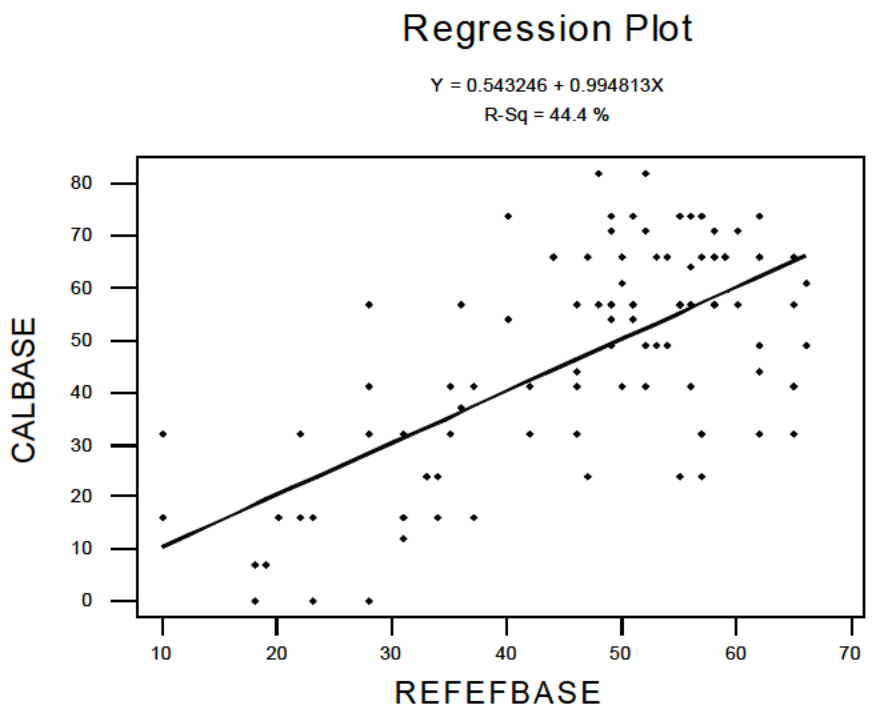
Results regarding the differences: Reference LVEF – Calibrated Echo LVEF:

(1): Reference LVEF- Calibrated Baseline Echo LVEF has Mean =0 ; Sigma = 13.2

(2): Reference LVEF - Calibrated 4mL Echo LVEF has Mean =0 ; Sigma = 9.6

Thus, the Sonovue enhanced Echo improves LVEF accuracy slightly over baseline. *However, it is once more not clear that the indicated reduction in "noise" is clinically significant.*

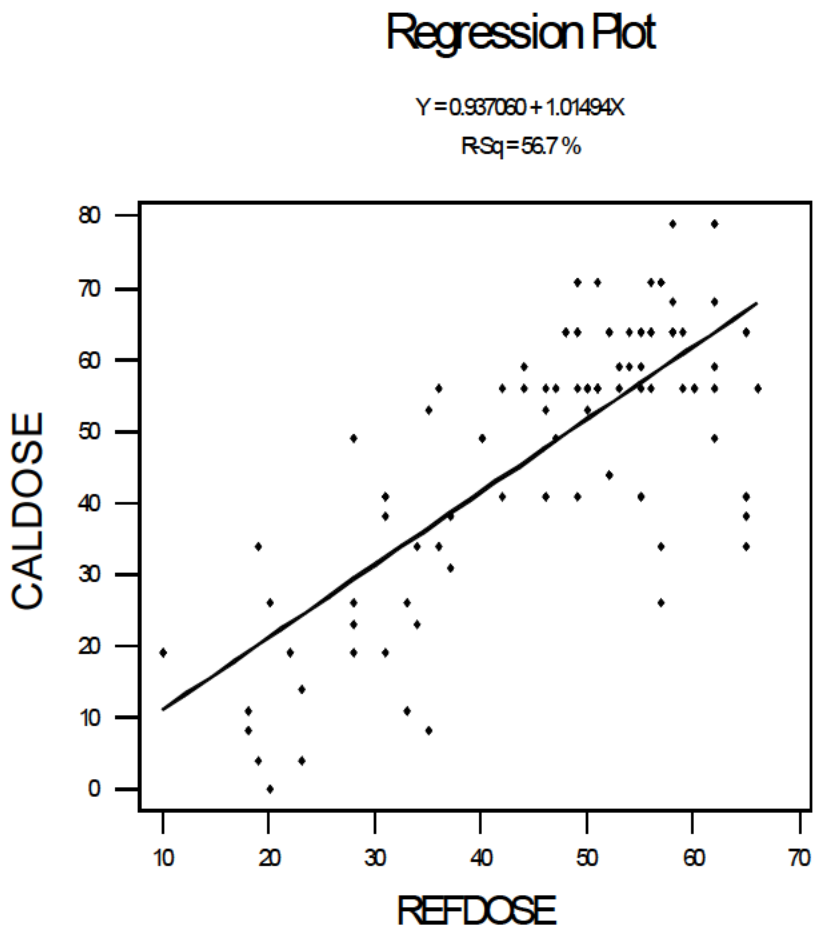
PLOT(A3)
Baseline Echo LVEF vs Reference LVEF
BR1-013
N = 53 Patients (106 reads – Baselines for 1mL and 2mL)



Note: Baseline reads are Calibrated to Regress around 45 Degree Line

Correlation = .67 Precision = Residuals = 15.7

PLOT(A4)
Enhanced Echo LVEF vs Reference LVEF
BR1-013
N = 53 Patients (106 reads – Enhanced for 1mL and 2mL)

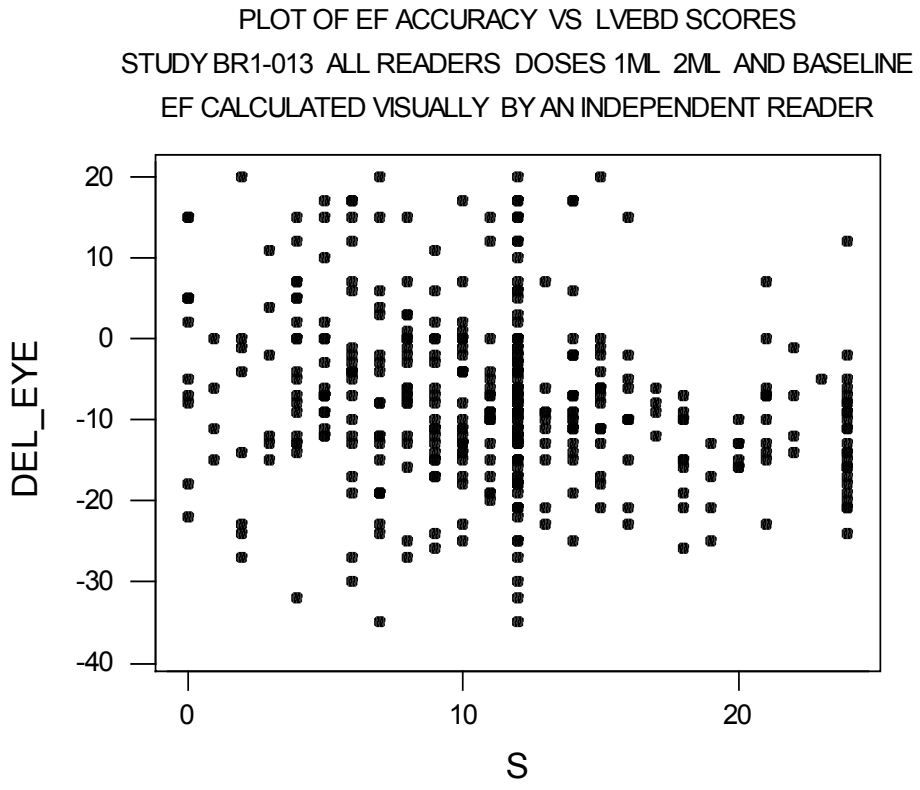


Note: Enhanced reads are Calibrated to Regress around 45 Degree Line

Correlation = .75 Precision = Residuals = 12.5

Conclusion concerning Plot(A3) and Plot(A4): Calibrated Enhanced Echo LVEF provides a slight statistical improvement in Accuracy over Calibrated Baseline Echo LVEF
(Correlation = .75 at Baseline versus Correlation = .67 at Enhancement, and Residual = 15.7 at Baseline versus Residual = 12.5 at Enhancement.)

Plot(A5)



Comments:

DEL_EYE = Reference LVEF – "Visual" Echo LVEF

S = LVEBD Score

Conclusion: There is no correlation between LVEBD and LVEF Accuracy.

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/s/

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Mike Welch
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BIOMETRICS
Concur with review