CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203684Orig1s000

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING PRODUCTS

Medical Officer's Resubmission Safety Review

NDA:	**203684**
Sponsor:	**Bracco Diagnostics Inc.**
Product:	**Lumason [Sulfur Hexafluoride Microbubbles]**
Reviewer:	Scheldon Kress, MD, DMIP/ODEIV/ OND/CDER
Today's Date:	June 10, 2014

Introduction

The Original Integrated Summary of Safety (ISS) included in the New Drug Application (NDA) 203-684 (Original NDA ISS) contained complete safety data for 70 completed studies (8 of which were conducted in healthy volunteers and 62 conducted in patients), with a data cut-off date of September 30, 2011, as well as the results of the safety evaluations in a pulmonary hemodynamic study in patients with and without pulmonary hypertension (BR1-133), and a comparative study with contrast-enhanced multidetector computed tomography (CE-MDCT)/ magnetic resonance imaging (MRI) in subjects with advanced hepatocellular carcinoma (HCC) (BR1-129), which had been completed, but not integrated into the pooled safety database. The 4-Month Safety Update was supplemental to the Original NDA ISS, as it included the results of Studies BR1-133 and BR1-129 integrated into the overall safety database as of January 31, 2012.

An additional Safety Update submitted to the FDA on May 31, 2013, also supplemental to the Original NDA ISS, included the results of the 2 studies integrated in the 4-Month Safety Update as mentioned above and 3 additional studies (1 for myocardial perfusion assessment [BR1-125], 1 in guidance of prostate biopsy [BR1-127], and 1 for the comparison of three-dimensional [3D] versus two-dimensional [2D] echocardiography [SonoV/BRA/013]), all reported as ongoing in the Original NDA ISS, which had been completed and integrated into the overall safety database as of December 31, 2012. Results for 1 completed observational study (BR1-132) were also presented

On November 4, 2013, the Food and Drug Administration informed Bracco of its acceptance of the name "Lumason" for the product proposed for approval under this NDA. However, the current Safety Update, also being provided as a supplement to the Original NDA ISS in response to the Complete Response Letter dated November 27, 2013 from the Division, presents summary safety data on the completed nonclinical and clinical studies conducted under the product name "SonoVue". No study, nonclinical or clinical, has been completed since the submission of the last Safety Update (submitted to the Division in May of 2013 with data cut-off date of December 31, 2013, hereafter referred to as May 2013 Safety Update). Results for the 2 remaining ongoing clinical studies (BR1-128 and BR1-130; focal liver lesion characterization) presented originally in the Original NDA ISS and again in the subsequent safety updates were not available as of the

cut-off date for this report (September 30, 2013). Post-marketing surveillance (PMS) and safety data reported in literature for SonoVue are presented as of September 30, 2013.

Safety Update from Clinical Studies

As of the data cut-off date of this updated Update (September 30, 2013), 9 cases of serious adverse events were reported among the 677 subjects dosed in the 2 ongoing Bracco-Sponsored clinical studies. Of these 9 cases, 7 occurred before the submission of the NDA 203-684 and were presented in the Original NDA ISS, whereas 2 cases occurred after the NDA submission and are presented here:

> **Case US-007303** (Study BR1-130, Patient No. 1625, SonoVue 2.4 mL): a 75-year-old male with a history of hypertension, high cholesterol, edema in bilateral legs, blood clots, arrhythmia, CAD, intermittent chest pain, insomnia, pacemaker placement, and an endoscopic biopsy of the pancreas to diagnose an Islet cell tumor, experienced extreme pain more than 24 hours after SonoVue-enhanced ultrasound-guided liver biopsy. The subject was admitted to the hospital for observation. A computed tomography (CT) was performed which revealed a hemorrhage into the lower parenchyma of the right lobe and additional hemorrhage extending into the renal parenchyma (reported as "hemorrhage right liver lobe"). The subject was considered to be stable, and to have recovered from the hemorrhage (without surgery, other intervention or transfusion) and was released from the hospital 2 days later. The Investigator considered the event to be related to the liver biopsy, not the administration of SonoVue.
>
> **Case FR-000791** (Study BR1-130, Patient No. 3003, SonoVue 2.4 mL), a 64-year-old female patient received SonoVue for an ultrasound to study focal liver lesions. The day after the procedure she presented with rectal hemorrhage (reported as "rectorrhagia") which led to hospitalization. The event recovered without treatment. The patient had history of diverticular sigmoiditis treated by sigmoidectomy, performed about a week before receiving SonoVue. The investigator considered the event not to be related to the administration of SonoVue, but a consequence of the previously performed surgery.

Safety Update from Post-marketing Surveillance

Post-marketing surveillance data received in the period of April 1, 2001 through September 30, 2013 from the countries where SonoVue is marketed are summarized.

SonoVue was first approved in 15 European Union countries under the centralized procedure on 26 March 2001. SonoVue is currently registered in 39 countries worldwide. Since the submission of the Original NDA ISS, SonoVue has been registered or marketed in 3 additional countries (Croatia on July 1, 2013, Russian Federation on August 5, 2013, and Brazil on September 30, 2013).

Based on sales statistics, with each unit sold representing one patient exposed to SonoVue, an estimated (b) (4) patients were exposed to SonoVue from October 1, 2011 through September 30, 2013. A total of 98 of these patients reported serious adverse reactions (reporting rate: (b) (4)

- 98 new serious adverse reaction cases reported since the Original NDA ISS submission
  - 62 were allergy-like or anaphylactoid in nature
  - 43 were cardiac-related
  - 4 deaths

Four fatal outcomes were reported among the (b) (4) patients newly exposed to SonoVue during the 2-year period following the submission of the Original NDA ISS. Four other patients experienced serious adverse events and subsequently died due to other causes. Narratives for these cases were provided.

Overall, experience from post-marketing surveillance of the estimated (b) (4) patients exposed to SonoVue from April 1, 2001 through September 30, 2013 during the market use of this product, shows that:

- Reporting rate of serious adverse events after administration of SonoVue is low (361/(b) (4) exposed patients; (b) (4)) and has remained unchanged since the Original NDA Submission

- Observed pattern of serious adverse event cases possibly related to the administration of SonoVue is similar to that reported for anaphylactic or anaphylactoid reactions to other intravascular imaging agents;

- Serious hypersensitivity reactions are observed in approx. 1 in 10,000 exposures;

- Overall reporting rate of fatal cases during SonoVue market use is low (18/(b) (4) exposed patients; (b) (4)) and favorably comparable with the risk for fatal events reported for iodinated contrast agents (approximately 0.001%).

Table A: Comparison of Safety Data from Post-Marketing Surveillance for (b) (4)

	Original NDA Submission	4-Month Safety Update	Safety Update (2-year period)	Cumulative Data Available as of September 30, 2013
Timeframe	April 1, 2001 to September 30, 2011	October 1, 2011 to January 31, 2012	October 1, 2011 to September 30, 2013	April 1, 2001 to September 30, 2013
Estimated Exposure*	(b) (4)			
Serious Adverse Events [a]	251 (b) (4)	19 (b) (4)	105 (b) (4)	361 (b) (4)
Serious Adverse Reactions [b]	246 (b) (4)	19 (b) (4)	98 (b) (4)	346 (b) (4)
Fatal Cases [c]	9 (b) (4) [d]	0 [e]	4 (b) (4) [f,g,h]	13 (b) (4) [d,e,f,g,h]
Fatal Cases Where Association with SonoVue Could Not be Ruled Out [i]	6 [j]	0	2	8 [j]

* By Company convention, the estimate of sales/exposure figures of the data lock point month is considered to be identical to that of the month immediately prior. Thus, the total number of patients exposed for each reporting period column (excluding the 4-Month Safety Update column as it is accounted for in the Safety Update (2-year period) column) does not add up to the Cumulative Data column.

a Number of cases with serious adverse events (including cases with fatal outcome) regardless of association with the administration of SonoVue.

b Number of cases with serious adverse events (including cases with fatal outcome) for which association with the administration of SonoVue could not be ruled out.

c All cases of fatal outcome, regardless of Reporter and Bracco causality assessment.

d One additional case of death (GB-000374) was reported for a patient who experienced serious adverse events of ventricular fibrillation and cardiac arrest during a stress echocardiogram with unknown outcome and subsequently died 19 days after the administration of SonoVue. Both events were considered to be unrelated to the administration of SonoVue.

e One additional case of death (DE-000911) was reported for a patient who experienced anaphylactic shock, considered to be related to SonoVue administration, and recovered completely after 28 days. Three weeks after the recovery, the patient died due to cardiac disease.

f One additional case of death (IT-002146) was reported for a patient who experienced serious adverse events of bleeding in the left carotid artery and acute respiratory insufficiency 12 hours after the administration of SonoVue; both events were considered to be unrelated.

g One additional case of death (DE-001447) was reported for a patient who experienced serious adverse events of hypersensitivity (considered related to SonoVue administration) and pulmonary embolism (considered unrelated to SonoVue administration) from which the outcome was considered to be unknown; however, the patient subsequently died 3 days later due to multi-organ failure.

h One additional case of death (ES-000813) was reported for a patient who experienced a serious adverse event of acute renal failure, considered to be unrelated to SonoVue administration, from which he did not recover and subsequently died 6 days later.

i Count based on Bracco's continued medical assessment of each fatal case following a response to the Request for Information received from the Division on April 24, 2013.

j Included 3 cases with causality of "unassessable" at the time of Original NDA submission. Upon receipt of additional information and further medical review, the causal role of the administration of SonoVue could not be ruled out for 2 of the cases.

Post-marketing Surveillance Death Cases

Since the submission of the Original NDA ISS, 4 new cases with fatal outcome have been received by the Sponsor for a total of 13 deaths (b) (4) reported during post-marketing use of SonoVue (since the launch of the product in 2001). The association of the deaths with Lumason administration could not be ruled out in 8 of the 13 cases; there was no relation to Lumason reported for the remaining 5 cases.

In addition to these 13 patients, 5 other patients experienced serious adverse events after the administration of Lumason and subsequently died. Among these 5 patients, 1 patient experienced a serious adverse event of anaphylactoid shock with recovered/resolved outcome, considered to be related to the administration of Lumason, and subsequently died almost 7 weeks later due to their underlying cardiac disease, 1 other patient experienced an allergic reaction considered to be related to the administration of Lumason with an unknown outcome, and subsequently died 3

days later following multi-organ failure (unrelated to the administration of Lumason), 1 patient who experienced serious adverse events of bleeding in the left carotid artery and acute respiratory insufficiency 12 hours after the administration of Lumason; both events were considered to be unrelated, 1 patient who experienced serious adverse events of hypersensitivity (considered related to Lumason administration) and pulmonary embolism (considered unrelated to Lumason administration) from which the outcome was considered to be unknown; however, the patient subsequently died 3 days later due to multi-organ failure, and 1 patient who experienced a serious adverse event of acute renal failure, considered to be unrelated to Lumason administration, from which he did not recover and subsequently died 6 days later. Narratives for 10 of the 18 patients were provided in the Original NDA ISS; the 8 remaining cases were provided in this update.

Safety Data Reported in the Literature

A literature search was performed according to the criteria listed in Section 3.1.9 of the Original NDA ISS on January 14, 2013 to identify any newly published (between October 1, 2011 and September 30, 2013) supportive evidence of the safety of intravenous Lumason administration during echocardiography and non-cardiac ultrasound studies. This search yielded 46 additional articles, 11 of which were considered to be relevant. Two of the published articles demonstrated the use of Lumason in the Cardiac Population and 9 were included among the Non-Cardiac Population. No serious or non-serious adverse events were reported in the 11 recently published Articles.

Medical Reviewer's Comments

Estimated number of patients exposed to SonoVue during the market use of the product:

(b) (4) Patients exposed to Lumason included in the Original NDA ISS submission

(b) (4) Patients newly exposed to Lumason during the 2-year period following the submission of the Original NDA ISS.

(b) (4) Total number of patients exposed to Lumason during product marketing.

Administration of Lumason, similar to other intravenously administered microspheres, has the potential to be associated with the rare immediate onset of serious life-threatening anaphylactic and anaphylactoid reactions. Both serious adverse events and adverse events with a fatal outcome either related or not to Lumason administration, occurred infrequently. The data provided within this safety update did not reveal any significant increase in the incidence of Lumason-related serious life-threatening events.

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/s/

SCHELDON KRESS
06/11/2014

BRENDA Q YE
06/11/2014

DIVISION OF MEDICAL IMAGING PRODUCTS
Medical Officer's Review of Request from
Division of Medication Error Prevention and Analysis

NDA:	**203684**
Sponsor:	**Bracco Diagnostics Inc.**
Product:	**Lumason**
Medical Reviewer:	Scheldon Kress, MD, DMIP/ODEIV/ OND/CDER
Requestor:	Neil Vora, PharmD, MBA *Safety Evaluator* Division of Medication Error Prevention and Analysis (DMEPA) FDA/CDER/Office of Surveillance and Epidemiology
Project Manager:	Frank Lutterodt, DMIP/ODEIV/ OND/CDER
Through:	Libero Marzella MD, Director, DMIP/ODE IV/ OND/CDER
Submission Date:	**May 29,, 2014**
Today's Date:	**May 31, 2014**

Division of Medication Error Prevention and Analysis (DMEPA) Request for Information

"I am a safety evaluator from the Division of Medication Error Prevention and Analysis and I am reviewing the labels and labeling for Lumason. Based on my review I have several questions. In Dosage and Administration Section, Recommended Dose, Bracco states that the recommended dose of Lumason should be 2 mL. With other injectable products in other areas (e.g., hematology, oncology, rheumatology, etc.), we are accustomed to putting mg amount for dosing instead of volume amount. However, I realize that with imaging products use of the volume amount may be a common practice. As a result, I have a question related to this: in your practical experience what would you recommend, keeping the dose in mL amount or revising this to the dose in milligrams?

Additionally, since this product is injected as bolus and Bracco does not have "Administration" Section in Dosage and Administration, we are assuming that Lumason should be injected into the IV line that is already established for the patient. Is that correct? If not, do you think "Administration" section should be added to the Dosage and Administration Section explaining the administration procedure?

Finally, as part of reconstitution steps, it states that Lumason should be reconstituted under aseptic conditions. From a pharmacy perspective, it means this reconstitution process should follow USP Chapter <797> and reconstituted under the laminar hood. However, based on your clinical experience, will that be the case or where and how do you anticipate this product will be reconstituted for administration given the fact that this is a suspension after reconstitution that needs to be re-agitated again if not administered immediately?"

Neil Vora, PharmD, MBA Safety Evaluator

DMIP Response

Concern #1

From a practical standpoint utilizing the 2 cc volume dose is ideal. Microbubble suspension administration is always measured by volume.

Concern #2

Regarding the Reconstitution (Dosage and Administration Section) Section

In the PI are illustrations of the Reconstitution Kit designed for preparation of the suspension aseptically at the bed-side. We believe the instructions are clear, easy to follow and can be adequate performed aseptically at the bed-side.

However, comparing the TEXTs of the 3 microbubble labels regarding aseptic preparation one finds the following discrepancies.

Therefore, we will now propose language for Lumason similar to that utilized for Definity.

	Lumason	Definity	Optison
Current label	Perform all Lumason reconstitution steps under aseptic conditions.	It is essential to follow directions for activation of Definity carefully and to adhere to strict aseptic procedures during preparation.	[no specific wording related to aseptic handling]
Proposed Label Revision	**It is essential to follow directions for activation of Lumason carefully and perform all Lumason reconstitution steps using aseptic procedures.**		

Concern #3

Lumason can be injected IV either directly into a vein or into an IV access port or line that is already established for the patient.

DMIP Recommended Action -

Label Revision:

2.2 DOSAGE AND ADMINISTRATION

Reconstitution steps:

~~*Perform all Lumason reconstitution steps under aseptic conditions.*~~
It is essential to follow directions for activation of Lumason carefully and perform all Lumason reconstitution steps using aseptic procedures.

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/s/

SCHELDON KRESS
06/03/2014

BRENDA Q YE
06/03/2014

MEMORANDUM DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 11/22/2013
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, Office of Drug Evaluation-IV
To: File, NDA-203684
Subject: Complete Response for NDA 203684, Lumason (Sulfur Hexafluoride Lipid Microsphere)

This is the ODE memo to concur with the decision to issue a Complete Response (CR) for this NDA, as recommended by the Division of Medical Imaging Products (DMIP, referred to as the Division in this memo). Lumason is a contrast agent for echocardiogram, to be indicated for use to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

This submission is deficient in several critical elements related to CMC data and cGMP compliance in the manufacturing facility. These deficiencies cast serious doubt about the consistency in quality of the product. While other review disciplines have not identified any other serious issues, this NDA cannot be approved before the deficiencies summarized in the CR letter are resolved satisfactorily. This conclusion reached by the Division is concurred by this Office.

The regulatory history of this drug's development has been summarized in the Division Director's memo by Dr. Marzella. This drug has been marketed in the European Union since 2001 and an NDA was submitted to US FDA in the same year. That submission was withdrawn after pharmacovigilance reports of serious cardiopulmonary reactions including fatalities in the EU.

The current NDA was first submitted in on 12/20/2011, and was issued a CR on 10/1/2012 for inspection deficiencies at the applicant's facility in Europe and the concern that the root cause of imaging failure in European postmarketing reports remained unresolved. There were also questions about the lyophilization procedure and characterization of the transfer device. This NDA was resubmitted on 5/21/2013.

Major issues of this NDA are summarized as follows, a complete list of all CR deficiencies will be provided in more detail in the action letter.

I. Efficacy and Safety of Lumason

The efficacy of Lumason for the proposed indication was based on three studies that demonstrated the ability of sulfur hexafluoride lipid microspheres to improve the left ventricular endocardial border delineation, which have been evaluated and affirmed in the last review cycle. There is no new data presented in this re-submission that may change the previous conclusion.

Likewise for safety, extensive review of clinical studies and published reports by the medical review team indicates no change in the safety profile of Lumason. As summarized by Dr. Marzella, the overall incidence of adverse reactions in clinical trials was approximately 5%, mostly were non-specific (e.g. headache, nausea, chest pain and discomfort), mild and resolved spontaneously.

The rare but serious hypersensitivity and cardiopulmonary reactions including fatalities in postmarketing reports have been extensively reviewed and discussed at two Advisory Committee meetings (2008 and 2011) for the two ultrasound contrast agents marketed in the US and for Lumason. There have been no new reports over the past several years.

Lumason does not seem to increase the risk of serious or fatal events in critically ill patients undergoing echocardiography. Experience from post-marketing surveillance of the estimated (b) (4) patients who have received Lumason shows a total of 335 serious adverse reactions for a reporting rate of (b) (4)

A boxed warning describes the serious cardiovascular reactions and the anaphylactoid reactions are described in the warnings section of the label. No additional safety studies other than standard surveillance are considered necessary.

There are no new findings of other review disciplines that may affect the above efficacy/safety assessments. Results of inspection on clinical data in the previous review cycle have been acceptable. Previous conclusions for approval reached by the reviewers of pharmacology/toxicology, clinical pharmacology, and microbiology still stand. With regard to the transfer device, a CR issue in the last cycle, the new Mini-Spike transfer device for reconstitution of Lumason was found to be acceptable by the CDRH consult reviewer and is supported by a cleared 510(k) application.

II. CMC & GMP

The resubmission has not adequately addressed critical deficiencies identified in the previous review cycle. As a result, the FDA district office and the Office of Compliance (OC) have issued a withhold recommendation, which is concurred by this Office.

The CMC reviewer Dr. Salazar has determined that additional manufacturing and control procedures critical for the quality of the final lyophilized product had been developed to address the inspectional deficiencies identified in the previous review cycle. However, inspection by the OC showed that the NDA has not been updated to reflect the incorporation of these changes. As described by the OC inspector/reviewer, Dr. Rose, the applicant needs to include a revised version of the batch records in the NDA once the compliance deficiencies are resolved.

Failure of imaging has been reported with some batches, we need documented assurance that the changes in CMC process and facilities have been implemented and the new measures will be indeed corrective.

III. The Quality Deficiencies in Risk/Benefit Assessment

The efficacy and safety of this imaging agent have been established and thus the clinical benefit and risk are acceptable. The decision to issue a CR on the basis of CMC/GMP issues for this NDA must take the following into consideration.

There are other similar products approved and available for the same indication (Optison and Definity) on the market. This new agent offers no significant advantage in efficacy and/or safety over the older drugs. There is therefore no public health urgency to make this agent available for an unmet medical need.

It should be noted that the product is approved in Europe and continued to be manufactured and marketed in that region. While such marketing history provides some

assurance on the quality and therapeutic consistency, product failure did occurred and the clinical implication cannot be dismissed lightly.

Whether the deficiencies can be resolved post marketing depends on the clinical setting how this product will be used. If the potential defect in its quality may lead to imaging failure, which has been reported in Europe, then the failure must not put the patients at risk and should be correctable without serious time constrain. The imaging failure will be recognized immediately and, in an elective procedure, different batch or alternative agent may be used. However, in other settings, cardiac imaging with Lumason may be studied in patients under medical emergency, then the uncertainty in its quality will be less tolerable.

Thus the deficiencies in CMC and GMP issues for this NDA should be corrected before approval for marketing.

IV. The Path Forward

For the product to be approvable in the next review cycle, the sponsor needs to follow the instruction in the CR letter and address all the deficiencies identified. The applicant has indicated in a pre-action meeting that it will comply with the requirements to resolve the CR.

V. Conclusions

The applicant has not adequately addressed the CMC/GMP deficiencies, and such deficiencies cast serious doubt about the product quality, which in turn may cause imaging study failure and place patient at risk in an emergency situation. Thus, Lumason cannot be approved before the deficiencies are resolved. A CR should be issued as recommended by the Division.

cc:
ORIG: NDA- 203684
Director, ODE-IV
Director, DMIP
Review Team, NDA-203684

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/s/

SHAW T CHEN
11/22/2013

DIVISION OF MEDICAL IMAGING PRODUCTS

Medical Officer's Resubmission Review

NDA:	**203684**
Sponsor:	**Bracco Diagnostics Inc.**
Product:	**[Sulfur Hexafluoride Microbubbles]**
Reviewer:	Scheldon Kress, MD, DMIP/ODEIV/ OND/CDER
Through:	Libero Marzella MD, Acting Director, DMIP/ODE IV/ OND
Today's Date:	October 17, 2013

Table of Contents

1. Introduction – Complete Response Letter

Bracco Diagnostics Inc. submitted New Drug Application (NDA) dated December 20, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoVue (Sulfur Hexafluoride) Microbubbles Injection.

FDA completed review of this application, as amended, and determined that it could not approve the application as provided. The FDA described the reasons for this action in their Complete Response Letter dated October 1, 2012 and, where possible, made recommendations to address specific issues:

LABELING

1. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

   To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

2. Please submit draft carton and container labeling revised as follows:
   a. Insert space between numeric value '5' and dosing units 'mL' in the statement [redacted (b) (4)] We recommend this revision to improve the readability of the amount of diluent needed.

FACILITY INSPECTIONS

3. During a recent inspection of the Bracco Suisse manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

RELATED APPARATUS

4. We were unable to locate the Mini-Spike [redacted (b) (4)] model in submission [redacted (b) (4)] Provide the fundamental differences between the [redacted (b) (4)] model and other devices cleared under [redacted (b) (4)]

5. Confirm if a [redacted] (b) (4) is incorporated in the Mini-Spike [redacted] (b) (4) transfer device.

6. Provide performance compatibility testing for the glass syringe and [redacted] (b) (4)

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a re-tabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4) Therefore, you must submit a protocol that is adequate to assess the safety and effectiveness in all relevant pediatric subgroups for this proposed indication.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

2. Bracco's Response to FDA's CR Letter [Dated 5- 31- 2013]

Bracco provided a specific response document which addressed each of the deficiencies and comments raised by FDA in their October 19, 2012 letter. For each deficiency or comment, supporting information is included as an attachment to the response document or as additional or revised sections for Modules 1, 2, 3, and 5. Appropriate links to these supporting documents are contained within the response document.

With regard to the Proprietary Name, Bracco acknowledged that the name SonoVue was not considered to be acceptable. Within the response submission, Bracco included an

amended Request for Proprietary Name Review.

Bracco also submitted a Safety Update which included responses to the specific FDA questions 1 thru 7 concerning the safety update. In response to question 8, English language versions of foreign labeling have been included.

Bracco provided responses to the FDA Complete Response Letter to their Original New Drug Application (NDA) 203-684: SonoVue (sulfur hexafluoride lipid microsphere) Kit for Preparation of Injectable Suspension received on October 19, 2012.

Each FDA issue is reproduced here within boxed text followed by a Bracco Response to address the issue and if not immediately addressed in the provided text, the location NDA section within the resubmitted e-CTD NDA.

Only the clinically–related deficiencies will be addressed in this review.

LABELING

Deficiency 5. Submit revised draft labeling that incorporates the text within the attached labeling example. If you identify typographical or formatting errors within this labeling example, please correct these errors within your response. Supply information to justify any substantive changes to the labeling text. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes. For the reason outlined below, the attached labeling uses an "X" as a placeholder for your proposed proprietary drug name.

Bracco Response:

Bracco submitted a revised draft labeling that incorporates the FDA proposed text provided in the Complete Response Letter. Typographical and formatting errors within the labeling example were corrected within their response. They supplied information to justify any substantive changes to the labeling text. Further, they are

submitting an updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as required in Module 1 of the e-CTD NDA.

PROPRIETARY NAME

As described in our letter of September 17, 2012, your drug's proposed proprietary name (Sonovue) was unacceptable. If you intend to have a proprietary name for your drug, we recommend that you submit a new request for a proposed proprietary name review.

Bracco Response:

Bracco submitted an AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW for the name (b) (4) on January 8, 2013 under our active IND 46,958 as we intend to have a proprietary name for our drug. On April 9, 2013 FDA notified Bracco our two submitted proposed Proprietary names were found to be unacceptable. Therefore, Bracco submitted two new proposed names for review under an AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- **Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.**
- **Present tabulations of the new safety data combined with the original NDA data.**
- **Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.**
- **For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.**

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Bracco Response:

Bracco provided a safety update as described at 21 CFR 14.50(d)(5)(vi)(b) which addresses questions 1 to 7 of the Safety Update section of the Complete Response Letter.

Bracco originally provided a copy of their European label "Summary of Product Characteristics" to IND 46,958 serial number 368 on August 13, 2010 which is the

basis of all European Union labeling. In addition, they provided English versions of the product labeling for our review from Canada, China, India, Hong Kong, Singapore, South Korea and Switzerland. This information can be found in Module 1 Section 1.15.5 of the resubmitted NDA.

3. Medical Officer's Prior Safety Summary – 1-6-2011 [Based on Submission Dated 8-13-2010]

A total of 10 deaths were reported in all the clinical studies conducted with SonoVue from 1993 to Jan 6, 2011. All of these deaths were considered to be unrelated to the administration of SonoVue. Nine fatalities have been reported within the postmarketing surveillance since the launch of the product. Three deaths were considered to be probably related, four deaths were considered to be possibly related to the administration of SonoVue and two deaths were considered to be unrelated to the administration of SonoVue.

Within 70 clinical trials, 6723 subjects have been dosed with SonoVue. 5275 subjects were exposed to SonoVue in completed studies and 1448 patients have been dosed within ongoing studies. Twenty-one SAEs were observed among completed studies and 9 SAEs among ongoing studies (total = 30). Two of these cases experienced onset of symptoms typical of anaphylaxis approximately 1 minute post SonoVue administration. In another case a subject experienced suggestive symptoms of anaphylaxis immediately following administration of both dipyridomole and SonoVue, thus making it more difficult to pin-point the causative agent.

Spontaneously reported serious adverse events and deaths (including events from observational and investigator initiated studies), regardless of the causal relationship, received in the period of April 1, 2001 through July 28, 2010 from the countries where SonoVue was marketed were summarized. Whereas the spontaneous reporting system is a voluntary system of reporting adverse events, reports often do not contain diagnoses, but simply describe the signs and symptoms that occurred, or may include preliminary diagnoses and incomplete information.

Among the estimated (b) (4) patients exposed to SonoVue during the market use of the product, deaths were reported for 9 patients and serious spontaneous events were reported for 207 patients (adverse event reporting rate: (b) (4)). Of the 207 cases, 204 cases were considered related to SonoVue administration. Of the 207 SAE cases, 159 involved reports coded to the "Immune System Disorders" SOC (reporting rate: (b) (4)), 57 involved reports coded to the "Cardiac Disorders" SOC (reporting rate: (b) (4)), 42 reports coded to "Nervous disorders" SOC (reporting rate: (b) (4)), 39 reports coded to "Vascular disorders" SOC (reporting rate: (b) (4)) and 33 reports coded to the "Respiratory, thoracic and mediastinal disorders" SOC (reporting rate (b) (4)). Both adverse events with a fatal outcome and serious adverse events occurred infrequently post administration of SonoVue.

The sponsor provided listings for 159 immune-mediated serious cases.

Of the 6723 patients dosed in clinical trials with SonoVue to date, 8 patients (0.1 %) had serious adverse events with the specified symptoms most frequently associated with serious life-threatening reactions to administration of intravenous microspheres; 5 (five) patients had events with the symptoms that were considered unrelated to SonoVue administration, and 3 patients had events that were considered related. Symptoms observed included: asystole, cardiogenic shock, anaphylactic shock, ST elevation, dyspnea, circulatory collapse, hypotension and shock.

Medical Officer's Recommendations

Whereas administration of SonoVue, similar to other intravenously administered microspheres, has the potential to be associated with the immediate onset of serious life-threatening events, physicians administering these agents may need guidance in management of these SAEs involving the immune, cardiac, vascular, respiratory, and nervous systems. As demonstrated in the case reports of deaths provided, when confronted with such emergencies in patients with known coronary artery disease, clinicians have had difficulty distinguishing cardiac from anaphylactic causation, thus impeding timely initiation of proper therapeutic measures. Availability of this information may be beneficial in providing guidance to assist clinicians when suddenly faced with such medical emergencies.

Deaths during Clinical Trials

A total of 10 deaths have been reported in all the clinical studies conducted with SonoVue from 1993 to January 6, 2011. Brief summaries for each patient who died in clinical trials is listed here. All deaths were considered to be unrelated to study agent by both the investigators and Bracco.

FDA Conclusion

A total of 10 deaths (nine from completed studies and one from ongoing studies) were reported in the clinical trials conducted with SonoVue. All of these deaths can be considered unrelated to the administration of SonoVue. In particular:

- 1 patient died before receiving SonoVue
- 2 patients had procedural complications during percutaneous coronary interventions following. a well-tolerated echocardiographic exam with SonoVue
- 1 patient died after undergoing right hepatectomy
- 6 patients died 10 to 26 days after exposure to SonoVue. In none of these six cases did the death follow any reaction or complication related to the administration of SonoVue

Cases with Fatal Outcome Reported in Postmarketing Surveillance (N=9)

This section summarizes the 9 deaths that occurred during spontaneous reporting from launch of the product to January 6, 2011. Three deaths occurred before 2005, six in 2005 or later. Narrative summaries for each case were provided. **Table 1** summarizes the medical narratives, onset of fatal adverse events and reviewer's assessment of likely causality.

FDA Conclusion

Of the 9 reported deaths, 2 cases (BCM-000767 and BRO-008552) appear to be clearly unrelated to the administration of SonoVue. Four (4) cases (BRO-005943 Germany, BRO-006772 Germany NL-000008 Netherlands, and CN-000162 China) were possibly related to the administration of SonoVue. Several cases provided only limited information.

The remaining three (3) cases (BRO-011933 Norway, DE-000545 Germany and DE-000635 Germany) demonstrated a similar pattern, an anaphylactic or anaphylactoid reaction immediately (seconds to minutes) following the intravascular administration of SonoVue. In general, the observed pattern of these cases considered as probably related to the administration of SonoVue are very similar to that reported with other intravenous medical imaging agents. Symptoms start a few seconds or minutes after contrast administration. Sometimes the events start with mild symptoms and then a drop in blood pressure, dyspnea and/or loss of consciousness are observed; sometimes they are already severe from the beginning. Of note, no skin or mucosal symptoms were ever observed in these cases. In all cases, underlying conditions of the patients may have contributed the fatal outcome. Thee patients suffered from significant coronary artery disease. In two cases (BRO-005943 and NL-000008), SonoVue was administered to patients with ongoing acute myocardial infarctions. Of note, in both cases no specific treatment for the underlying myocardial infarction was given, but only treatment for anaphylaxis.

Table 1
Summary of Fatal Outcomes Reported in Postmarketing Surveillance

Case ID/ Country	Medical Narratives – Fatal Outcomes	AE Onset Post CUS			Causality
		Sec	Min	Hours	
BRO-005943* Germany	Patient with myocardial infarction developed bradycardia, hypotension, loss of consciousness & ventricular fibrillation post second CUS for stent occlusion. Died same day.		4-5		**Possible**
BRO-006772 Germany	Patient with myocardial infarction post angioplasty developed loss of consciousness & asystole post CUS. Died 40 min post CUS.		?		**Possible**
BCM-000767 Italy	Patient following PTCA developed irreversible cardiac arrest post CUS. Autopsy finding complete thrombosis common coronary trunk		2		Unrelated
BRO-008552 Sweden	Patient developed loss consciousness, dyspnea & abdominal pain few min post morphine injection post liver CUS			9	Unrelated
BRO-011933* Norway	Patient developed dyspnea, cough & strange taste, unconsciousness, seizure post CUS for liver metastases. Failed resuscitation. Died 40 min post CUS.	15			**Probable**
NL-000008* Netherlands	Patient developed anaphylactic reaction & sudden death post CUS while a myocardial infarction was evolving. Died 40 min post CUS.		2		**Possible**
DE-000545* Germany	Patient developed anaphylactic reaction/ shock and acute myocardial infarction post CUS. Died 40 min post CUS.	30			**Probable**
DE-000635* Germany	Patient developed anaphylactoid reaction post CUS for unknown indication. Died same day.		1		**Probable**
CN-000162* China	Patient developed cough & nausea, shock & coma post liver CUS for anorexia.	40-60	<1		**Possible**

? = Exact minutes after unknown CUS = contrast enhanced ultrasound
* = Cases with narratives provided

4. Summary Sponsor's Safety Update – 10-3-2013 [Submitted 5-31-2013 as Response to CR Letter]

Introduction

The Original Integrated Summary of Safety (ISS) included in the New Drug Application (NDA) 203-684 (from here on out referred to as *Original NDA ISS*) contained complete safety data for 70 completed studies (8 of which were conducted in healthy volunteers and 62 conducted in patients), with a data cut-off date of September 30, 2011, as well as the results of the safety evaluations in a pulmonary hemodynamic study in patients with and without pulmonary hypertension (BR1-133), and a comparative study with contrast-enhanced multidetector computed tomography (CE-MDCT)/magnetic resonance imaging (MRI) in subjects with advanced hepatocellular carcinoma (HCC) (BR1-129), which had been completed, but not integrated into the pooled safety database. The *4-Month Safety Update* was supplemental to the *Original NDA ISS*, as it included the results of Studies BR1-133 and BR1-129 integrated into the overall safety database as of January 31, 2012.

The current Safety Update is supplemental to the *Original NDA ISS.* This report includes the results of the 2 studies integrated in the *4-Month Safety Update* as mentioned above and 3 additional studies (1 for myocardial perfusion assessment [BR1-125], 1 in guidance of prostate biopsy [BR1-127], and 1 for the comparison of three-dimensional [3D] versus two-dimensional [2D] echocardiography [SonoV/BRA/013]) reported as ongoing in the *Original NDA ISS* which have been completed and integrated into the overall safety database as of December 31, 2012.

Also presented in this Safety Update are the results for 1 completed observational study (BR1-132). Results for the remaining 2 ongoing studies (BR1-128 and BR1-130; focal liver lesion characterization) presented originally in the *Original NDA ISS* and again in the *4-Month Safety Update* were not available as of the cut-off date for this safety update (December 31, 2012). Post-marketing surveillance (PMS) is also updated as of December 31, 2012.

On April 24, 2013, a Request for Information (RFI) was received by Bracco from the Division of Medical Imaging Products regarding Bracco's March 29, 2013 submission of Safety Report Identification GB-BRACCO-000695 to Investigational New Drug application (IND) 46,958. A response to this request was submitted to the IND on May 3, 2013. An overall summary of the information provided in the response is also presented in this document for completeness.

The Sponsor provided more detailed data in four Appendices. Appendix 1 provides a tabular summary of all completed and ongoing clinical trials as of December 31, 2012. Appendix 2 provides adverse events by system organ class (SOC) and preferred term (PT) for subjects administered SonoVue in All Completed Studies. Narratives of subjects who died, had serious adverse events, or discontinued participation in a study due to an adverse event as of September 30, 2011 were provided in Appendix 3 of the *Original*

NDA ISS. Narrative summaries for each of the patients who died, experienced serious adverse events or discontinued participation in a clinical trial due to an adverse event for the 5 studies completed since the submission of the *Original NDA ISS* are provided in Appendix 3 of this document. Adverse events by SOC and PT for subjects administered with SonoVue in Completed Cardiac Studies are provided in Appendix 4.

5. Safety Data for Newly Exposed Subjects – October 1, 2011 through December 31, 2012

Recently Completed Clinical Trials

Five clinical trials have been completed during the period of October 1, 2011 to December 31, 2012.

This safety update focuses on integrated information for:

- **All Patients in Completed Studies,**
- **All Patients in Completed Cardiac Studies,**
- **All Completed Microvasculature Studies,**
- **Special Patient Population Studies** and
- **All Completed Studies** (including Healthy Volunteers and Patients)

As was reported in the *Original NDA ISS*, 1 of the 30 patients dosed in the Microvasculature Population study BR1-129 and 3 of the 36 patients dosed in the Special Patient Population study BR1-133 collectively reported 4 non-serious adverse events. The relationship to the administration of SonoVue could not be ruled out by the Investigator for 2 of the 4 events (both were considered to be of unknown relation to the administration of SonoVue). No serious adverse events or deaths were reported, and no patient discontinued the study due to an adverse event. Seventy-four (74) of the 628 patients dosed in the Cardiac Population study BR1-125 and 20 of the 273 patients dosed in the Microvasculature Population study BR1-127 collectively reported 123 non-serious adverse events. Four patients from Study BR1-125 and 1 patient from Study BR1-127 reported 5 serious adverse events (1 each), only 1 of which the relationship to the administration of SonoVue could not be ruled out by the Investigator. One patient in Study BR1-125 died due to arterial rupture following ballooning of the left main artery; the cause of death was considered by the Investigator to be unrelated to the administration of SonoVue.

Six patients discontinued study participation due to an adverse event reported during the Study BR1-125; no patient discontinued due to an adverse event reported during Study BR1-127.

One additional serious adverse event was reported outside of the protocol-defined reporting window (from the time of signed Informed Consent through 24 hours post-dose) for Study BR1-127; the event was reported during the study, but worsened after the

patient completed the study. The event was considered to be unrelated to the administration of SonoVue both when it was reported during the study (non-serious) and again after the study was completed (serious). Only 1 patient out of 65 patients dosed in the Cardiac Population study BRA/013 reported 1 adverse event considered by the Investigator to be serious and probably related to the administration of SonoVue for which study participation was discontinued. No other adverse events were reported, and no patient died during this study.

Recently Completed Observational Studies

One observational study (BR1-132) completed during the 15-month period since the submission of the *Original NDA ISS*. SonoVue Study BR1-132 was a retrospective analysis investigating in hospital mortality (within the same day as or the calendar day following performance of the echocardiography procedure) rate in 757 critically ill patients undergoing echocardiography with the administration of SonoVue in comparison with 3087 patients undergoing echocardiography without contrast agent.

Ongoing Clinical Trials

Two clinical trials (BR1-128 and BR1-130) completed patient enrollment between October 1, 2011 and December 31, 2012; however, study assessments (blinded reads) were still ongoing as of the data cut-off date for this update. Since the submission of the *Original NDA ISS,* 323 patients with focal liver disease were dosed with SonoVue for the characterization of focal liver lesions in Studies BR1-128 (no new training patients and 89 new efficacy patients) and BR1-130 (15 new training patients and 206 new efficacy patients) for a total of 677 patients dosed between the 2 studies. Among the 323 patients newly dosed with SonoVue, 2 patients in Study BR1-130 reported 2 serious adverse events of which both were considered by the Investigator to be unrelated to the administration of SonoVue.

Post-marketing Surveillance

SonoVue has not been registered or marketed in any additional countries in the 15-month period since the submission of the *Original NDA ISS*.

Based on sales statistics, with each unit sold representing one patient exposed to SonoVue, an additional estimated (b) (4) patients were exposed to SonoVue from October 1, 2011 through December 31, 2012. A total of 59 of these patients reported serious adverse reactions (reporting rate: (b) (4)). Of the 59 new serious adverse reaction cases reported since the *Original NDA ISS* submission, 42 were allergy-like or anaphylactoid in nature and 24 were cardiac-related as determined either solely by the Reporter, or by an internal medical review performed by Bracco.

Two fatal outcomes were reported among the (b) (4) patients newly exposed to SonoVue during the 15-month period following the submission of the *Original NDA*

ISS. One other patient experienced bleeding in the left carotid artery together with acute respiratory insufficiency, both considered to be unrelated to the administration of SonoVue, and subsequently died. Narratives for these cases were provided.

Since the data cut-off of this Safety Update, a RFI was received from the Division on April 24, 2013 regarding Bracco's March 29, 2013 submission of Safety Report Identification GB-BRACCO-000695 to IND 46,958. This case involves a 62-year-old male patient with currently stable coronary disease who, 2 minutes after receiving 2.1 mL of SonoVue, reported feeling unwell with tingling in the arm and back, suspected by the reporter to be an anaphylactic reaction. Treatment for anaphylaxis was administered without benefit. The patient then experienced a grand mal seizure, became unresponsive and went into cardiac arrest from which resuscitation was unsuccessful. The request was for Bracco to provide follow-up information (narrative was provided) and an autopsy report for this case, in addition to a narrative for all deaths and serious adverse events reported since the submission of the *4-Month Safety Update*. **Table 2** displays the incidence of reported serious adverse events and cases of death reported for the *Original NDA Submission*, the *4-Month Safety Update*, the time between the cut-off date of the *4-Month Safety Update* until the date the RFI was received, in addition to the cumulative data.

Table 2
Comparison of Safety Data from Post-Marketing Surveillance for SonoVue

	Original NDA Submission	4-Month Safety Update	Data Available as of Receipt of RFI	Cumulative Data Available as of Receipt of RFI
Timeframe	April 1, 2001 to September 30, 2011	October 1, 2011 to January 31, 2012 (4 months)	February 1, 2012 to April 24, 2013 (14.5 months)	April 1, 2001 to April 24, 2013 (12 years)
Estimated Exposure	(b) (4)			
Serious Adverse Events [a]	251	19	65	335
Serious Adverse Reactions [b]	246	19	61	326
Fatal Cases [c]	9 [d]	0[e]	3 [f]	12 [d,e,f]
Fatal Cases Where Association with SonoVue Could Not be Ruled Out [g]	6[h]	0	1	7[h]

a Serious adverse events (including cases with fatal outcome) regardless of association with the administration of SonoVue.
b Serious adverse events (including cases with fatal outcome) for which association with the administration of SonoVue could not be ruled out.
c All cases of fatal outcome, regardless of Reporter and Bracco causality assessment.
d One additional case of death was reported for a patient who experienced serious adverse events of ventricular fibrillation and cardiac arrest during a stress echocardiogram with unknown outcome and subsequently died 19 days after the administration of SonoVue. Both events were considered to be unrelated to the administration of SonoVue.
e One additional case of death was reported for a patient who experienced anaphylactic shock, considered to be related to SonoVue administration, and recovered completely after 28 days. Three weeks after the recovery, the patient died due to cardiac disease.
f One additional case of death was reported for a patient who experienced serious adverse events of bleeding in the left carotid artery and acute respiratory insufficiency 12 hours after the administration of SonoVue; both events were considered to be unrelated.
g Count based on Bracco's medical assessment of each fatal case as requested in the RFI of April 24, 2013.
h Includes 3 cases with causality of "unassessable".

Overall, experience from post-marketing surveillance of the estimated (b) (4) patients exposed to SonoVue from April 1, 2001 through April 24, 2013 during the market use of this product, shows that:

- the reporting rate of serious adverse events after administration of SonoVue is low (335/(b) (4) exposed patients; (b) (4)) and has remained unchanged since the *Original NDA Submission*;
- the observed pattern of serious adverse event cases possibly related to the administration of SonoVue is similar to that reported for anaphylactic or anaphylactoid reactions to other intravascular imaging agents (serious hypersensitivity reactions are observed in approx. 1 in 10,000 exposures);
- the overall reporting rate of fatal cases during SonoVue market use is (12/(b) (4) exposed patients; (b) (4)) comparable with the risk for fatal events reported for iodinated contrast agents (approximately 0.001%).

Safety Data Reported in the Literature

A literature search was performed on December 31, 2012 to identify any newly published (between October 1, 2011 and December 31, 2012) supportive evidence of the safety of intravenous SonoVue administration during echocardiography and non-cardiac ultrasound studies. This searches yielded 37 additional articles, 11 of which were considered to be relevant. Two of the published articles demonstrated the use of SonoVue in the Cardiac Population and 9 were included among the Non-Cardiac Population. There were no serious or non-serious adverse events reported in the 11 recently published articles Cardiac and Non Cardiac Populations.

6. Cumulative Safety Data through December 31, 2012

The *Original NDA ISS* provided a cumulative safety assessment of SonoVue as of September 30, 2011 including the results of the safety evaluations for 70 completed clinical trials that comprised the pooled integrated safety database for the clinical program conducted in North America, Europe, and Asia.

Since the submission of the *Original NDA ISS*, 5 additional studies have been integrated into the pooled safety database. Therefore, included in this Safety Update are the results of the safety evaluations for the 6307 subjects who received SonoVue and/or control agents in the 75 completed clinical trials that comprise the pooled integrated safety database for the clinical program conducted in North America, Europe, and Asia as of December 31, 2012.

Summary tables of disposition, exposure, demographics, and adverse event rates, which include data from the newly completed studies, have been produced for the categories of

- **Completed Cardiac Studies,**
- **Complete Microvasculature Studies,**
- **All Completed Studies in Patients**
- **All Completed Studies** (including Healthy Volunteers and Patients),

The values in these tables have been compared with the corresponding values from the *Original NDA ISS*. For the purposes of integrated analysis, the completed clinical studies were categorized as described in **Table 3** below.

The following data are pooled and summarized for All Completed Clinical Studies (including Healthy Volunteers and Patients), and All Completed Studies in Patients (i.e., excluding subjects in the Healthy Volunteer Studies), All Completed Cardiac Studies and All Completed Microvasculature Studies:

- disposition;
- study agent exposure;
- demographic and baseline characteristics;
- adverse events, overall and study agent-related.

In addition, brief results are presented from:

- Completed observational study (BR1-132)
- Safety data from 2 ongoing studies
- Data from 2 studies conducted in Japan

Data from 2 prospective observational studies were presented in the *Original NDA ISS*. **Table 3** provides a brief description of the safety studies included within the overall SonoVue clinical program.

Table 3
Bracco-Sponsored Clinical Safety Studies in the Clinical Program by Completion Status and Study Type

Completion Status Study Type Patient Population	No. of Studies (Total = 86)
Completed studies included in the Integrated SonoVue Safety Database	*75 studies*
Healthy Volunteer Studies[a] – BR1-001, BR1-002, BR1-007, BR1-008, BR1-009, BR1-010[b], BR1-025, BR1-110[b]	*8 studies*
Patient Studies	*67 studies*
Cardiac Population – BBG-001, BBG-012, BR1-005, BR1-006, BR1-011, BR1-012, BR1-013, BR1-019A, BR1-019B, BR1-020, BR1-021, BR1-027, BR1-029, BR1-038, BR1-041, BR1-056, BR1-063, BR1-066, BR1-068, BR1-103, BR1-104, BR1-112, BR1-113, BR1-122, **BR1-125, BRA-013**	26
Macrovasculature Population – BR1-014, BR1-017, BR1-023A, BR1-023B, BR1-031, BR1-040, BR1-049, BR1-051, BR1-106	9
Microvasculature Population – BBG-003, BBG-006, BR1-015, BR1-018, BR1-032, BR1-033, BR1-034, BR1-035, BR1-039, BR1-042, BR1-043, BR1-045, BR1-048, BR1-052, BR1-053, BR1-067, BR1-071, BR1-072, BR1-100, BR1-105, BR1-118, BR1-121, **BR1-127**, **BR1-129**, BRA-007, IGIT-002, IGIT-005, IGIT-008	28
Special Patient Populations Patients with Congestive Heart Failure – BR1-016 Patients with Chronic Obstructive Pulmonary Disease – BR1-022 Patients with Diffuse Interstitial Pulmonary Fibrosis – BR1-036[b] Patients With or Without Pulmonary Hypertension – **BR1-133**	4
Completed studies presented separately in the NDA; not part of the Integrated SonoVue Safety Database	*9 studies*
Rechallenge: Macro- and microvascular patients with prolonged enhancement – BR1-026	1
Case-Control: Investigation of idiosyncratic/allergy-like reactions – BR1-124	1
Retrospective Studies Retrospective ECG studies in cardiac patients – BR1-109, BR1-111	2
Observational Studies Prospective: SonoVue AWB 08 Observational post-marketing study in patients in South Korea – OBS-BIK-001 Retrospective: SonoVue **BR1-132 (in-hospital mortality in critically ill patients)**	3
Completed Japanese Studies Study E7210-J081-001 and Study E7210-J081-002	2
Ongoing Bracco-sponsored clinical studies Patients with focal liver disease – BR1-128, BR1-130	*2 studies*

[a] Clinical pharmacokinetic and pilot efficacy studies in non-patient volunteers.
[b] Pharmacokinetic study.

Also summarized in this Safety Update are the spontaneous reporting of data during the PMS of SonoVue from April 1, 2001 to December 31, 2012 from outside the United States and the data reported in literature relevant to the safety of SonoVue.

Results – All Completed Studies (Healthy Volunteers and All Patients)

The numbers of unique subjects who received SonoVue and/or control agents in All Completed Studies are presented by category of study in **Table 4**.

Table 4
Summary of Completed SonoVue Studies Included in Pooled Safety Database

Population	*Original ISS*				*Safety Update*			
	No. of Studies	No. of Treated Subjects			No. of Studies	No. of Treated Subjects		
		SonoVue[a]	Control Only	Total		SonoVue[a]	Control Only	Total
All Completed Studies	70	5275	162	5437	75	6307	162	6469
Healthy Volunteers[b]	8	128	30[c]	158	8	128	30[c]	158
All Patients	62	5147	132	5279	67	6179	132	6311
Cardiac Population	24	1769	126[d]	1895	26	2462	126[d]	2588
Macrovascular Population	9	555	0	555	9	555	0	555
Microvascular Population	26	2785	0	2785	28	3088	0	3088
Special Patient Populations	3	38	6[c]	44	4	74	6	80

a Received SonoVue only or SonoVue plus control in crossover studies; included as SonoVue subjects in all summary data displays.
b Clinical pharmacokinetics and pilot efficacy studies in non-patient volunteers.
c Saline.
d Albunex and/or saline.

Subject Disposition

The disposition of All Subjects (healthy volunteers and patients) who participated in **All Completed Clinical Studies** is provided in **Table 5**. No notable difference was observed between disposition as reported in the *Original NDA ISS* and that reported in this Safety Update.

Table 5
Disposition of Subjects (Healthy Volunteers and Patients), All Completed Studies, SonoVue

Number of Subjects	*Original NDA ISS*	*Safety Update*
Enrolled (signed informed consent)	5315	6358
Discontinued Prior to Receiving Study Agent	35	46
Withdrawal of consent	7	7
Protocol violation	4	4
Other	24	35
Received Study Agent	5275*,a	6307*,a
Completed Study	5002 (94.8%)	5926 (94.0%)
Prematurely Discontinued	273 (5.2%)	381 (6.0%)
Adverse event	16 (0.3%)	23 (0.4%)
Lost to follow-up	4 (0.1%)	4 (0.1%)
Withdrawal of consent	37 (0.7%)	47 (0.7%)
Protocol violation	2 (<0.1%)	2 (<0.1%)
Other[b]	211 (4.0%)	302 (4.8%)
No reason specified	3 (0.1%)	3 (<0.1%)

* Percentages are based on the number of subjects dosed.
a Five additional patients from Study BBG-006 received commercial SonoVue and were, therefore, excluded from the integrated safety summaries.
b Adverse event was given as the description under 'Other' reason for premature study discontinuation for 1 patient in Study BBG-001. This patient is counted among the 16 subjects who discontinued the study prematurely due to an adverse event in *Patient Data Listing 2*.

For this Safety Update, a total of 6358 subjects were enrolled in the studies; 46 subjects discontinued prior to receiving SonoVue. Of the 6307 subjects who received SonoVue, 5926 (94.0%) completed the studies, while 381 (6.0%) discontinued prematurely (23 for adverse events, 4 were lost to follow-up, 47 for withdrawal of consent, 2 for protocol violations, 302 for other reasons [such as no treatment (including no surgery or no radio-frequency ablation)], and 3 with no reason specified).

Extent of Exposure to Study Agent

Extent of exposure to SonoVue in All Completed Studies (healthy volunteers and patients) is summarized in **Error! Not a valid bookmark self-reference.** No notable difference was observed between extent of exposure to SonoVue as reported in the *Original NDA ISS* and that reported in this Safety Update.

For the 6241 subjects in the All Completed Studies (healthy volunteers and patients) with exposure to SonoVue (5 mg/mL), the mean total volume administered was 10.53 mL (range: 0.2 to 161.3 mL). This includes subjects who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. Three additional subjects received SonoVue at an 'unknown' total volume.

Sixty-nine percent (69%) of the subjects received cumulative doses ranging from a total of >1 mL to 10 mL; approximately 94.5% received cumulative doses ranging from a total of >1 mL to 50 mL.

Table 6
Exposure to Study Agent (Healthy Volunteers and Patients), All Completed Studies, SonoVue

	Original NDA ISS	*Safety Update*
Total Volume SonoVue Administered (mL)		
N	5239	6241
Mean (SD)	10.32 (14.435)	10.53 (13.432)
Median	4.80	7.20
Range (Minimum, Maximum)	(0.2, 161.3)	(0.2, 161.3)
Cumulative Dose Categories		
≤1 mL	228 (4.4%)	232 (3.7%)
>1 to 5 mL	2468 (47.1%)	2637 (42.3%)
>5 mL to 10 mL	1336 (25.5%)	1657 (26.6%)
>10 mL to 50 mL	1091 (20.8%)	1599 (25.6%)
>50 mL	116 (2.2%)	116 (1.9%)

Only exposure to SonoVue 5 mg/mL is summarized. Study BR1-025 (N=33) is excluded since exposure was to SonoVue 15 mg/mL. Study BR1-129 (N=30) is excluded as the study was designed with multiple visits that were 2 to 8 weeks apart which is very different from all other studies being summarized. Three additional subjects received SonoVue at an 'unknown' total volume.
For summary exposure, undiluted volume was used. When diluted volume was administered, undiluted volume was computed for summary purposes.
Study BR1-006: 3 / 10 dilution was used.
Study BR1-008: 3 / 10 dilution was used.
Study BR1-021: 1 / 2 dilution was used for infusion administration.

Demographic and Baseline Characteristics

The demographic and baseline characteristics in All Completed Studies (healthy volunteers and patients) are summarized in **Table 7**. No notable difference was observed between demographic and baseline characteristics as reported in the *Original NDA ISS* and that reported in this Safety Update.

The majority of the 6307 subjects (healthy volunteers and patients) who received SonoVue in All Completed Studies were male (64.7%) and white (79.2%). The mean age was 59.2 years (range: 17 to 99 years), the mean weight was 74.99 kg (range: 35.0 to 210.0 kg), and the mean height was 169.29 cm (range: 118.0 to 204.0 cm). The majority of subjects were enrolled in studies conducted in Europe (69.9%) and received the marketed formulation of SonoVue (97.5%). The demographic and baseline characteristics were similar for the 6469 subjects who received investigational product (SonoVue or control) in the completed studies.

Table 7
Demographic and Baseline Characteristics, All Completed Studies (Healthy Volunteers and Patients)

	Original NDA ISS		*Safety Update*	
	SonoVue	Total [a]	SonoVue	Total [a]
Characteristic	N = 5275	N=5437	N=6307	N=6469
Gender, n (%)				
Male	3263 (61.9)	3385 (62.3)	4080 (64.7)	4202 (65.0)
Female	2011 (38.1)	2051 (37.7)	2226 (35.3)	2266 (35.0)
Unknown	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Age (years)				
<65, n (%)	3297 (62.5)	3408 (62.7)	3818 (60.5)	3929 (60.7)
≥65, n (%)	1976 (37.5)	2027 (37.3)	2487 (39.4)	2538 (39.2)
Unknown, n (%)	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
	(N=5273)	(N=5435)	(N=6305)	(N=6467)
Mean (SD)	58.3 (14.05)	58.1 (14.17)	59.2 (13.57)	59.0 (13.70)
Range (Minimum, Maximum)	17, 99	17, 99	17, 99	17, 99
Race, n (%)				
White	4058 (76.9)	4189 (77.0)	4993 (79.2)	5124 (79.2)
Black	159 (3.0)	177 (3.3)	192 (3.0)	210 (3.2)
Hispanic	33 (0.6)	39 (0.7)	33 (0.5)	39 (0.6)
Asian	1000 (19.0)	1003 (18.4)	1053 (16.7)	1056 (16.3)
Other	22 (0.4)	26 (0.5)	33 (0.5)	37 (0.6)
Unknown	3 (0.1)	3 (0.1)	3 (<0.1)	3 (<0.1)
Weight (kg)				
<75, n (%)	2855 (54.1)	2892 (53.2)	3262 (51.7)	3299 (51.0)
75 to 100, n (%)	2029 (38.5)	2116 (38.9)	2578 (40.9)	2665 (41.2)
>100, n (%)	286 (5.4)	324 (6.0)	361 (5.7)	399 (6.2)
Unknown, n (%)	105 (2.0)	105 (1.9)	106 (1.7)	106 (1.6)
	(N=5170)	(N=5332)	(N=6201)	(N=6363)
Mean (SD)	74.12 (15.922)	74.59 (16.438)	74.99 (15.887)	75.36 (16.304)
Range (Minimum, Maximum)	35.0, 210.0	35.0, 216.0	35.0, 210.0	35.0, 216.0
Height (cm)	(N=5160)	(N=5322)	(N=6191)	(N=6353)
Mean (SD)	168.90 (9.047)	169.05 (9.104)	169.29 (9.093)	169.40 (9.134)
Range (Minimum, Maximum)	120.0, 204.0	120.0, 204.0	118.0, 204.0	118.0, 204.0
Location of Study, n (%)				
Europe	3410 (64.6)	3438 (63.2)	4406 (69.9)	4434 (68.5)
North America	962 (18.2)	1096 (20.2)	998 (15.8)	1132 (17.5)
China	903 (17.1)	903 (16.6)	903 (14.3)	903 (14.0)
Formulation, n (%)				
Formulation 1	20 (0.4)	--	20 (0.3)	--
Formulation 2	60 (1.1)	--	60 (1.0)	--
Formulation 3	76 (1.4)	--	76 (1.2)	--
Final (Marketed) Formulation	5119 (97.0)	--	6151 (97.5)	--

[a] Includes subjects who received SonoVue and/or Control.
Table data derived from *Original NDA ISS End-of-Text Safety Table 3.1.1, and 12-Month Safety Update Table 3.1.*

7. Adverse Events

7.1 Overall Incidence of Adverse Events

Discussion of Adverse Events observed following administration of SF-6 will be subdivided into the following Sections:

7.2 All Completed Patients in Studies
7.3 All Completed Patients in Cardiac Studies
7.4 Completed Microvasculature Clinical Studies
7.5 Completed Observational Studies
7.6 Ongoing Clinical Trials
7.7 Post-marketing Surveillance
7.8 Safety Data Reported in the Literature
7.9 Special Safety Concerns

7.2 Results – All Completed Patients in Studies

Summary of Adverse Events Reported in the 5 Studies Completed Since the Submission of the Original NDA ISS

Five clinical trials were completed during the period of October 1, 2011 to December 31, 2012. An overall summary of the adverse events reported by the patients dosed in the 5 studies completed since the submission of the *Original NDA ISS* is presented in **Table 8**.

Among the 1032 patients included in the Safety Population of these studies, 103 (10.0%) reported 133 adverse events, of which 28 (2.7%) reported 40 adverse events considered by the Investigator to be of some relationship to the administration of SonoVue. The majority of events was mild in intensity and resolved without sequelae. Six patients (0.6%) reported 6 serious adverse events for which 2 were considered to be probably related to the administration of SonoVue and the rest unrelated. Seven patients (0.7%) discontinued study participation due to an adverse event. One patient died during Study BR1-125; the cause of death was considered to be unrelated to the administration of SonoVue.

Table 8
Summary of Adverse Events for Patients Dosed in the 5 Studies Completed Since the *Original NDA ISS*

	N=1032*	
	All	**Related[a]**
No. (%) of Patients Who Reported Adverse Events[b]	103 (10.0)	28 (2.7)
No. of Adverse Events Reported[c]	133	40
No. (%) of Patients Who Reported Serious Adverse Events	6 (0.6)[d]	2 (0.2)
No. (%) of Patients Who Discontinued Due to Adverse Events	7 (0.7)	5 (0.5)
No. (%) of Patients Who Died	1 (0.1)	0
No. (%) of Patients with at least 1 Non-serious Adverse Event by Intensity[e]	98 (9.5)	26 (2.5)
Mild Adverse Events	75 (7.3)	21 (2.0)
Moderate Adverse Events	23 (2.2)	5 (0.5)
Severe Adverse Events	0	0

* Percentages are based on the number of patients dosed.
[a] Includes adverse events with "definite", "probable", "possible", "doubtful", "unknown" and missing relationship to SonoVue.
[b] Includes all adverse events reported after first injection of SonoVue.
[c] Multiple occurrences of the same adverse event in a subject are counted individually.
[d] One additional patient, Patient No. 0610 of Study BR1-127, experienced a non-serious adverse event (prostatitis) during the study which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined adverse event reporting window.
[e] If a subject experienced more than 1 non-serious adverse event, the subject was counted only once at the maximum intensity.

Summary of All Adverse Events Reported in All Completed Studies (Healthy Volunteers and Patients), SonoVue

A summary of adverse events for All Completed Studies is presented in **Table 9**. Although the total number of patients dosed has increased, the relative incidence and percentages of AEs remained stable.

Of the 6307 subjects who received SonoVue in the All Completed Studies (including subjects who received SonoVue plus control in crossover studies), 675 (10.7%) experienced 1064 adverse events. Study agent-related adverse events were reported by 331 subjects (5.2%). The majority of events were mild and resolved without sequelae.

Nine subjects had adverse events that were considered severe in intensity (1 of which experienced hypertension and chills considered by the Investigator to be of 'unknown' relationship to study agent administration). Serious adverse events were reported for 27 subjects (0.4%); all except 5 events (2 of which had "unknown" relationship recorded in the clinical trial database, the third "probable" relationship; however subsequent information on all 3 cases suggests a possibility of no relationship to the investigational product) were considered to be not related to study agent. One additional subject experienced a non-serious adverse event during study participation, which became serious when the subject was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of

SonoVue at both recordings. Twenty three (23) subjects (0.4%) were discontinued due to adverse events, 12 of whom had events considered related to study agent.

Of the 28 patients with serious adverse events, a total of 10 deaths (0.1%) were reported in all completed clinical studies conducted with SonoVue since 1993. All 10 deaths were considered to be unrelated to study agent by both the Investigators and Bracco. Deaths occurred in both cardiac and non-cardiac studies. In particular:

- 1 patient had procedural complications during percutaneous coronary intervention (PCI) following well-tolerated echocardiographic exams with SonoVue;
- 1 patient had procedural complications during acute ballooning of the left main artery following well-tolerated echocardiographic exams with SonoVue;
- 1 patient died 3 days after SonoVue administration and shortly after undergoing right hepatectomy;
- 5 patients died 10 to 26 days after exposure to SonoVue. In none of these 5 cases did the death follow any reaction or complication related to the administration of SonoVue.

In addition, 1 patient who reported 2 serious adverse events during the clinical trial, subsequently died outside of the protocol-defined adverse event reporting window, and is, therefore, not included in the integrated safety database as a death. One other death was reported in the completed clinical studies for a patient who died of acute myocardial infarction before receiving SonoVue. As this was a pre-dose event, this patient is also not included in the integrated safety database as a death.

This total of 10 deaths is in agreement with the deaths reported from all completed clinical studies during the Safety Review sited in **Section 3. Medical Officer's Prior Safety Summary – 1-6-2011 [Based on Submission Dated 8-13-2010].** Each of these deaths considered to be unrelated to study agent by both the Investigators and Bracco is considered by this reviewer to also be unrelated to study agent. It is worth noting that the number of deaths stated in **Table 9** (provided by the Sponsor) does not accurately agree with the numbers provided in the text (10 deaths are described).

Table 9
Summary of Adverse Events, All Completed Studies (Healthy Volunteers and Patients), SonoVue

	Original NDA ISS		*Safety Update*	
	N=5275		N=6307	
Category	**Total**	**Related[a]**	**Total**	**Related[a]**
No. (%) of Subjects with at least 1 AE	572 (10.8)	303 (5.7)	675 (10.7)	331 (5.2)
No. (%) of Subjects with at least 1 Serious AE	21 (0.4)	3 (0.1)	27 (0.4)[b]	5 (0.1)
No. (%) of Subjects who Discontinued due to AEs	16 (0.3)	7 (0.1)	23 (0.4)	12 (0.2)
No. (%) of Deaths	7 (0.1)[c]	0	8 (0.1)[c]	0
No of AEs[d]	931	491	1064	531
No. (%) of Subjects with at least 1 Non-serious AE by Intensity:[e]	555 (10.5)	300 (5.7)	653 (10.4)	326 (5.2)
Mild AEs	446 (8.5)	260 (4.9)	521 (8.3)	281 (4.5)
Moderate AEs	100 (1.9)	39 (0.7)	123 (2.0)	44 (0.7)
Severe AEs	9 (0.2)	1 (<0.1)	9 (0.1)	1 (<0.1)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] One additional patient, Patient No. 0610 of Study BR1-127, experienced a non-serious adverse event (prostatitis) during the study which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined adverse event reporting window.
[c] One additional patient, who experienced 2 serious adverse events during the clinical trial, was reported to have died outside of the protocol-defined adverse event reporting window for Study BR1-071. One other death occurred in a patient who died of myocardial infarction before receiving SonoVue in Study BR1-020.
[d] Multiple occurrences of the same adverse event in a subject are counted individually.
[e] If a subject experienced more than 1 non-serious adverse event, the subject was counted only once at the maximum intensity.

Adverse Events by SOC and Preferred Term *Adverse Events Reported in the 5 Studies Completed Since the Submission of the Original NDA ISS*

The adverse events experienced most frequently (>0.5%) by the 1032 patients dosed in the 5 studies completed since the submission of the *Original NDA ISS* are summarized in **Table 10**. The most frequently reported adverse event was headache (23 patients, 2.2%), followed by chest pain (15 patients, 1.5%), nausea (7 patients, 0.7%), electrocardiogram ST segment depression (6 patients, 0.6%), and hypotension (6 patients, 0.6%). All other adverse events occurred at a frequency of <0.5%. Headache being the most frequently reported adverse event followed by nausea and chest pain is consistent with the overall reporting of events.

Table 10
Adverse Events by System Organ Class Reported in >0.5% of the Patients, 5 Studies Completed Since the *Original NDA ISS*, SonoVue

MedDRA System Organ Class/ Preferred Term	Number (%) of Patients (N=1032)*	
	All	Related[a]
Number (%) of Patients With Adverse Events[b]	103 (10.0)	28 (2.7)
Gastrointestinal Disorders		
Nausea	7 (0.7)	5 (0.5)
General Disorders and Administration Site Conditions		
Chest pain	15 (1.5)	2 (0.2)
Investigations		
Electrocardiogram ST segment depression	6 (0.6)	2 (0.2)
Nervous System Disorders		
Headache	23 (2.2)	3 (0.3)
Vascular Disorders		
Hypotension	6 (0.6)	2 (0.2)

* Percentages are based on the number of patients dosed.
AE/s = Adverse Event/s.
[a] Includes adverse events with "definite", "probable", "possible", "doubtful", "unknown" and missing relationship to SonoVue.
[b] Includes all adverse events reported after first injection of SonoVue.

All Adverse Events Reported in All Completed Studies (Healthy Volunteers and Patients), SonoVue

The adverse events experienced most frequently (>0.5%) by the 6307 subjects in All Completed Studies are summarized in **Table 11**. No notable difference is observed between adverse events reported in the *Original NDA ISS* and those reported in this Safety Update.

The most frequently reported adverse event was headache (132 subjects, 2.1%), followed by nausea (54 subjects, 0.9%), chest pain (48 subjects, 0.8%), and chest discomfort (31 subjects, 0.5%). All other adverse events occurred at a frequency of <0.5%.

Table 11
Adverse Events by System Organ Class Reported in >0.5% of the Subjects, All Completed Studies (Healthy Volunteers and Patients), SonoVue

MedDRA System Organ Class / Preferred Term	*Original NDA ISS* No. (%) of Subjects (N=5275)		*Safety Update* No. (%) of Subjects (N=6307)	
	Total	Related[a]	Total	Related[a]
No. (%) of Subjects with at least 1 AE	572 (10.8)	303 (5.7)	675 (10.7)	331 (5.2)
Gastrointestinal Disorders				
Nausea	47 (0.9)	29 (0.5)	54 (0.9)	34 (0.5)
General Disorders/Administration Site Conditions				
Chest discomfort	30 (0.6)	16 (0.3)	31 (0.5)	17 (0.3)
Chest pain	33 (0.6)	9 (0.2)	48 (0.8)	11 (0.2)
Injection site pain	26 (0.5)	20 (0.4)	26 (0.4)	20 (0.3)
Nervous System Disorders				
Headache	109 (2.1)	59 (1.1)	132 (2.1)	62 (1.0)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Serious Adverse Events and Adverse Events Resulting in Discontinuation

As mentioned above, 6 of the 1032 patients enrolled and dosed in the 5 completed studies newly integrated into the overall safety database reported 6 serious adverse events, and 7 patients discontinued participation in their respective study due to an adverse event.

Overall, 27 (0.4%) of the 6307 subjects administered with SonoVue had serious adverse events in the All Completed Studies. Of these 27 subjects, 22 subjects reported events that were considered unrelated to SonoVue administration. Four of the 5 cases possibly drug-related occurred in patients with cardiovascular diseases treated within cardiac studies including 1 case of chest pain associated with elevation of ST segment on electrocardiogram and hypotension (drug relationship initially reported as unknown, subsequent information indicated that the events were clearly related to ischemia triggered by dobutamine) and 1 case of skin rash (drug relationship probable) associated with vasovagal syndrome (drug relationship initially reported as probable, subsequent information indicated that the event was not directly related to the administration of SonoVue). The fifth patient reported sensory motor paresis (drug relationship reported as 'unknown'). One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings.

Eight of the 28 subjects with serious adverse events died. All deaths were considered to be unrelated to study agent. In addition, 1 patient who experienced 2 serious adverse events (considered by the Investigator to be unrelated to the administration of SonoVue) during a clinical trial died 2 weeks after completing the study; the occurrence of death was considered by the Investigator to be a result of the patient's underlying disease, and

not related to the administration of SonoVue. One other patient suffered a myocardial infarction and died prior to receiving SonoVue. Neither case of death is included in the integrated safety database.

Twenty-three (23; 0.4%) of the 6307 subjects administered with SonoVue discontinued due to adverse events in the All Completed Studies. Of these 23 subjects, 11 subjects reported events that were considered unrelated to SonoVue administration. The most commonly reported study agent-related adverse events resulting in discontinuation were hypotension reported by 4 subjects and nausea reported by 2 subjects (<0.1% each). All other study agent-related adverse events resulting in discontinuation occurred in 1 subject each.

Summary: All Completed Clinical Studies

The overall incidence of adverse events following administration of SonoVue in All Completed Studies (all subjects including Healthy Volunteers and Patients) was 10.7% (675/6307 subjects). The incidence of study agent-related adverse events was 5.2% (331/6307 subjects). The most frequently reported adverse event was headache, reported by 2.1% of subjects. Other adverse events reported by ≥0.5% of subjects included nausea (0.9%), chest pain (0.8%), and chest discomfort (0.5%). The majority of adverse events were mild in intensity and resolved without sequelae.

Serious adverse events were reported for 27 subjects (0.4%) who received SonoVue, 9 of whom died during or following study participation (8 deaths are captured in the integrated safety database, 1 is not). Of the 27 subjects with serious adverse events, 22 subjects reported events that were considered unrelated to SonoVue administration. Four of the 5 subjects with possibly drug-related serious adverse events were patients with cardiovascular diseases treated within cardiac studies including 1 case of chest pain associated with elevation of ST segment on electrocardiogram and hypotension (drug relationship initially reported as unknown, subsequent information indicated that the events were clearly related to ischemia triggered by dobutamine) and 1 case of skin rash (drug relationship probable) associated with vasovagal syndrome (drug relationship initially reported as probable, subsequent information indicated that the event was not directly related to the administration of SonoVue). The fifth patient reported sensory motor paresis (drug relationship unknown, thought to be related to underlying disease).

One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings. All 9 deaths were considered unrelated to SonoVue administration and did not follow any reaction or complication related to the administration of SonoVue. Twenty-three (23; 0.4%) subjects discontinued study participation due to adverse events, 12 of whom had adverse events considered related to study agent (doubtful, possible or probable relationship).

Patient Disposition

The disposition of All Completed Clinical Studies in Patients is provided in **Table 12**. No notable difference is observed between disposition as reported in the *Original NDA ISS* and that reported in this Safety Update. A total of 6230 patients were enrolled in the studies, with 46 patients discontinuing prior to receiving SonoVue. Of the 6179 patients who received SonoVue, 5801 (93.9%) completed the studies, while 378 (6.1%) discontinued prematurely (22 for adverse events, 4 were lost to follow-up, 47 for withdrawal of consent, 2 for protocol violations, 300 for other reasons, and 3 for no specified reason).

Table 12
Disposition of Patients, All Completed Studies in Patients, SonoVue

Number of Patients	*Original NDA ISS*	*Safety Update*
Enrolled (signed informed consent)	5187	6230
Discontinued Prior to Receiving Study Agent	35	46
Withdrawal of consent	7	7
Protocol violation	4	4
Other	24	35
Received Study Agent	5147[*,a]	6179[*,a]
Completed Study	4877 (94.8%)	5801 (93.9%)
Prematurely Discontinued	270 (5.2%)	378 (6.1%)
Adverse event	15 (0.3%)	22 (0.4%)
Lost to follow-up	4 (0.1%)	4 (0.1%)
Withdrawal of consent	37 (0.7%)	47 (0.8%)
Protocol violation	2 (<0.1%)	2 (<0.1%)
Other[b]	209 (4.1%)	300 (4.9%)
No reason specified	3 (0.1%)	3 (<0.1%)

[*] Percentages are based on the number of patients dosed.
[a] Five additional patients from Study BBG-006 received commercial SonoVue and were, therefore, excluded from the integrated safety summaries.
[b] Adverse event was given as the description under 'Other' reason for premature study discontinuation for 1 patient in Study BBG-001. This patient is counted among the 22 subjects who discontinued the study prematurely due to an adverse event in *Patient Data Listing 2*.

Extent of Exposure to Study Agent

Extent of exposure to SonoVue in All Completed Studies in Patients is summarized in **Table 13.** No notable difference is observed between extent of exposure to SonoVue as reported in the *Original NDA ISS* and that reported in this Safety Update.

For the 6146 patients in the completed studies with exposure to SonoVue, the mean total volume administered was 10.48 mL (range: 0.3 to 161.3 mL). This includes patients who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. Sixty-nine percent (69%) of the patients received cumulative doses ranging from >1 mL to 10 mL, with 94% having received cumulative doses ranging from >1 mL to 50 mL. Three additional subjects received SonoVue at an 'unknown' total volume.

Table 13
Exposure to Study Agent, All Completed Studies in Patients, SonoVue

	Original NDA ISS	*Safety Update*
Total Volume SonoVue Administered (mL)		
N	5144	6146
Mean (SD)	10.25 (14.469)	10.48 (13.447)
Median	4.80	7.20
Range (Minimum, Maximum)	0.3, 161.3	0.3, 161.3
Cumulative Dose Categories		
≤1 mL	220 (4.3%)	224 (3.6%)
>1 to 5 mL	2456 (47.7%)	2625 (42.7%)
>5 mL to 10 mL	1310 (25.5%)	1631 (26.5%)
>10 mL to 50 mL	1043 (20.3%)	1551 (25.2%)
>50 mL	115 (2.2%)	115 (1.9%)

Only exposure to SonoVue 5 mg/mL is summarized. Study BR1-129 (N=30) is excluded as the study was designed with multiple visits that were 2 to 8 weeks apart which is very different from all other studies being summarized. Three additional subjects received SonoVue at an 'unknown' total volume.

For summary exposure, undiluted volume was used. When diluted volume was administered, undiluted volume was computed for summary purposes.

Study BR1-006: 3 / 10 dilution was used for administration.

Study BR1-021: 1 / 2 dilution was used for infusion administration.

Table data derived from *Original NDA ISS End-of-Text Safety Tables 2.1.3 and 12-Month Safety Update Table 2.2.*

Demographic and Baseline Characteristics

The demographic and baseline characteristics in All Completed Studies in Patients is summarized in **Table 14.**. No notable difference is observed between demographic and baseline characteristics as reported in the *Original NDA ISS* and that reported in this Safety Update.

The majority of the 6179 patients dosed with SonoVue in the Completed Studies were male (64.4%) and white (78.9%). The mean age was 59.8 years (range: 17 to 99 years), the mean weight was 75.0 kg (range: 35.0 to 210.0 kg), and the mean height was 169.11 cm (range: 118.0 to 201.0 cm).

Table 14
Demographic and Baseline Characteristics, All Completed Studies in Patients, SonoVue

Characteristic	*Original NDA ISS* N = 5147	*Safety Update* N = 6179
Gender, n (%)		
Male	3164 (61.5)	3981 (64.4)
Female	1982 (38.5)	2197 (35.6)
Unknown	1 (<0.1)	1 (<0.1)
Age (yrs)		
<65, n (%)	3169 (61.6)	3690 (59.7)
≥65, n (%)	1976 (38.4)	2487 (40.2)
Unknown, n (%)	2 (<0.1)	2 (<0.1)
	(N=5145)	(N=6177)
Mean (SD)	59.0 (13.37)	59.8 (12.94)
Range (Minimum, Maximum)	17, 99	17, 99
Race, n (%)		
White	3939 (76.5)	4874 (78.9)
Black	156 (3.0)	189 (3.1)
Hispanic	32 (0.6)	32 (0.5)
Asian	996 (19.4)	1049 (17.0)
Other	21 (0.4)	32 (0.5)
Unknown	3 (0.1)	3 (<0.1)
Weight (kg)		
<75, n (%)	2794 (54.3)	3201 (51.8)
75 to 100, n (%)	1962 (38.1)	2511 (40.6)
>100, n (%)	286 (5.6)	361 (5.8)
Unknown, n (%)	105 (2.0)	106 (1.7)
	(N=5042)	(N=6073)
Mean (SD)	74.10 (16.031)	75.00 (15.978)
Range (Minimum, Maximum)	35.0, 210.0	35.0, 210.0
Height (cm)	(N=5032)	(N=6063)
Mean (SD)	168.68 (8.956)	169.11 (9.027)
Range (Minimum, Maximum)	120.0, 201.0	118.0, 201.0
Location of Study, n (%)		
Europe	3325 (64.6)	4321 (69.9)
North America	919 (17.9)	955 (15.5)
China	903 (17.5)	903 (14.6)

Overall Incidence of Adverse Events

A summary of adverse events for All Completed Studies in Patients is presented in **Table 15.** No notable difference is observed between adverse events reported in the *Original NDA ISS* and those reported in this Safety Update.

Of the 6179 patients who received SonoVue, 638 (10.3%) experienced 1008 adverse events. Study-agent related adverse events were reported by 302 patients (4.9%). The majority of events were mild and resolved without sequelae. Only 8 patients had adverse events that were considered severe in intensity (1 of which experienced hypertension and chills considered by the Investigator to be of 'unknown' relationship to study agent administration). Serious adverse events were reported for 27 patients (0.4%); all except 5 events (2 of which had "unknown" relationship recorded in the clinical trial database, and

a third of "probable" relationship; however subsequent information on all 3 cases suggests a possibility of no relationship to the investigational product) were considered to be not related to study agent. One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings. Eight (0.1%) of the 28 patients with serious adverse events died during the study; 1 additional patient died 2 weeks after the protocol-defined adverse event reporting window was closed and is therefore, not included in the integrated safety database as a death. None of the 8 deaths were considered related to study agent. One other patient suffered a myocardial infarction and died prior to receiving SonoVue. Twenty-two patients (0.4%) were discontinued due to adverse events, 11 of whom had events considered to be related to the administration of SonoVue.

Table 15
Summary of Adverse Events, All Completed Studies in Patients, SonoVue

	Original NDA ISS		*Safety Update*	
	No. (%) of Patients (N=5147)		No. (%) of Patients (N=6179)	
Category	Total	Related[a]	Total	Related[a]
No. (%) of Patients with at least 1 AE	535 (10.4)	274 (5.3)	638 (10.3)	302 (4.9)
No. (%) of Patients with at least 1 Serious AE	21 (0.4)	3 (0.1)	27 (0.4)[b]	5 (0.1)
No. (%) of Patients who Discontinued due to AEs	15 (0.3)	6 (0.1)	22 (0.4)	11 (0.2)
No. (%) of Deaths	7 (0.1)[c]	0	8 (0.1)[c]	0
No of AEs[d]	875	449	1008	489
No. (%) of Patients with at least 1 Non-serious AE by Intensity[e]	518 (10.1)	271 (5.3)	616 (10.0)	297 (4.8)
Mild AEs	413 (8.0)	233 (4.5)	488 (7.9)	254 (4.1)
Moderate AEs	97 (1.9)	37 (0.7)	120 (1.9)	42 (0.7)
Severe AEs	8 (0.2)	1 (<0.1)	8 (0.1)	1 (<0.1)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] One additional patient, Patient No. 0610 of Study BR1-127, experienced a non-serious adverse event (prostatitis) during the study which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined adverse event reporting window.
[c] One additional patient, who experienced 2 serious adverse events during the clinical trial, was reported to have died outside of the protocol-defined adverse event reporting window for Study BR1-071. One other death occurred in a patient who died of myocardial infarction before receiving SonoVue in Study BR1-020.
[d] Multiple occurrences of the same adverse event in a patient are counted individually.
[e] If a patient experienced more than 1 non-serious adverse event, the patient was counted only once at the maximum intensity.

Adverse Events by SOC and Preferred Term

The adverse events experienced most frequently (>0.5%) by the 6179 patients in All Completed Studies in Patients are summarized in **Table 16**. No notable difference is observed between adverse events reported in the *Original NDA ISS* and those reported in this Safety Update.

The most frequently reported adverse event was headache (125 patients, 2.0%), followed by nausea (53 patients, 0.9%), chest pain (48 patients, 0.8%), and chest discomfort (30 patients, 0.5%). All other adverse events occurred at a frequency of <0.5%.

Table 16
Adverse Events by System Organ Class Reported in >0.5% of the Patients, All Completed Studies in Patients, SonoVue

MedDRA System Organ Class / Preferred Term	*Original NDA ISS* Number (%) of Patients (N=5147)		*Safety Update* Number (%) of Patients (N=6179)	
	Total	Related[a]	Total	Related[a]
No. (%) of Patients with at least 1 AE	535 (10.4)	274 (5.3)	638 (10.3)	302 (4.9)
Gastrointestinal Disorders				
Nausea	46 (0.9)	29 (0.6)	53 (0.9)	34 (0.6)
General Disorders/Administration Site Conditions				
Chest discomfort	29 (0.6)	15 (0.3)	30 (0.5)	16 (0.3)
Chest pain	33 (0.6)	9 (0.2)	48 (0.8)	11 (0.2)
Injection site pain	24 (0.5)	18 (0.3)	24 (0.4)	18 (0.3)
Nervous System Disorders				
Headache	102 (2.0)	53 (1.0)	125 (2.0)	56 (0.9)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Summary: All Completed Patients in Clinical Studies

Of the 6179 patients who received SonoVue, 638 (10.3%) experienced 1008 adverse events. Study agent-related adverse events were reported by 302 patients (4.9%). The majority of events were mild and resolved without sequelae. Only 8 patients had adverse events that were considered severe in intensity (1 of which experienced hypertension and chills considered by the Investigator to be of 'unknown' relationship to study agent administration). Serious adverse events were reported for 27 patients (0.4%); all except 5 events (2 of which had "unknown" relationship recorded in the clinical trial database, and a third of "probable" relationship; however subsequent information on all 3 cases suggests a possibility of no relationship to the investigational product) were considered to be not related to study agent. Twenty-two patients (0.4%) were discontinued due to adverse events, 11 of whom had events considered related to study agent. One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings.

Of the 28 patients with serious adverse events, a total of 10 deaths (0.1%) were reported in all completed clinical studies conducted with SonoVue since 1993. All 10 deaths were considered to be unrelated to study agent by both the Investigators and Bracco. Deaths occurred in both cardiac and non-cardiac studies. In particular:

- 1 patient had procedural complications during percutaneous coronary intervention (PCI) following well-tolerated echocardiographic exams with SonoVue;
- 1 patient had procedural complications during acute ballooning of the left main artery following well-tolerated echocardiographic exams with SonoVue;
- 1 patient died 3 days after SonoVue administration and shortly after undergoing right hepatectomy;
- 5 patients died 10 to 26 days after exposure to SonoVue. In none of these 5 cases did the death follow any reaction or complication related to the administration of SonoVue.

In addition, 1 patient who reported 2 serious adverse events during the clinical trial, subsequently died outside of the protocol-defined adverse event reporting window, and is therefore, not included in the integrated safety database as a death. One other death was reported in the completed clinical studies for a patient who died of acute myocardial infarction before receiving SonoVue. As this was a pre-dose event, this patient is also not included in the integrated safety database as a death.

7.3 Results – All Completed patients in Cardiac Studies

As of the cut-off date for this Safety Update (December 31, 2012), 2 studies in the cardiac population have been newly completed (i.e., final CTR available). Study BR1-125 was a Phase III, open-label, non-randomized study conducted to compare SonoVue-enhanced myocardial contrast echocardiography (MCE) with electrocardiogram (ECG)-gated single photon emission computerized tomography (SPECT), at rest and at peak of low-dose dipyridamole stress test, in the assessment of significant coronary artery disease (CAD; coronary stenosis ≥ 70%) in 628 patients with known or suspected CAD, with quantitative coronary angiography as the gold standard. Study BRA/013 was a Phase IV, multicenter, open-label, intra individual comparison conducted in 65 patients who received SonoVue intravenously using the Vueject injector, to prove the non-inferiority of SonoVue-enhanced 3D echocardiography to SonoVue-enhanced 2D echocardiography (apical 2-chamber view and 4-chamber view) for the assessment of global left ventricular function defined by cardiac MRI and to compare all imaging techniques, including cardiac MRI, in the analysis of regional left ventricular function to a gold standard defined by a consensus read. Both studies have been integrated into the pooled safety database and are, therefore, reported amongst the cumulative data provided below.

Patient Disposition

The disposition of all patients who participated in the Completed Cardiac Studies is provided in **Table 17**. A total of 2476 patients were enrolled in the studies, with 14 patients discontinuing prior to receiving SonoVue. Of the 2462 patients who received SonoVue, 2290 (93.0%) completed the studies, while 172 (7.0%) discontinued

prematurely (18 for adverse events, 1 was lost to follow-up, 13 for withdrawal of consent, and 140 for other reasons).

Table 17
Disposition of Patients, Completed Cardiac Studies, SonoVue

Number of Patients	*Original NDA ISS*	*Safety Update*
Enrolled (signed informed consent)	1781	2476
Discontinued Prior to Receiving Study Agent	12	14
Other	12	14
Received Study Agent	1769*	2462*
Completed Study	1694 (95.8%)	2290 (93.0%)
Prematurely Discontinued	75 (4.2%)	172 (7.0%)
Adverse event	11 (0.6%)	18 (0.7%)
Lost to follow-up	1 (0.1%)	1 (<0.1%)
Withdrawal of consent	3 (0.2%)	13 (0.5%)
Other	60 (3.4%)	140 (5.7%)

* Percentages are based on the number of patients dosed.

Extent of Exposure to Study Agent

As shown in **Table 18**, for the 2459 patients in the Completed Cardiac Studies with exposure to SonoVue, the mean total volume administered was 15.66 mL (range: 0.5 to 161.3 mL). This includes patients who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. Fifty-three percent (53%) of the patients received cumulative doses ranging from >1 mL to 10 mL, with 94% having received cumulative doses ranging from >1 mL to 50 mL.

Table 18
Exposure to Study Agent, Completed Cardiac Studies, (b) (4)

	Original ISS	*Safety Update*
Total Volume SonoVue Administered (mL)		
N	1766	2459
Mean (SD)	16.39 (20.738)	15.66 (17.854)
Median	7.50	8.70
Range (Minimum, Maximum)	0.5, 161.3	0.5, 161.3
Cumulative Dose Categories		
≤1 mL	55 (3.1%)	59 (2.4%)
>1 to 5 mL	466 (26.4%)	471 (19.2%)
>5 mL to 10 mL	650 (36.8%)	828 (33.7%)
>10 mL to 50 mL	494 (28.0%)	1000 (40.7%)
>50 mL	101 (5.7%)	101 (4.1%)

Only exposure to SonoVue 5 mg/mL is summarized.
For summary exposure, undiluted volume was used. When diluted volume was administered, undiluted volume was computed for summary purposes.
Study BR1-006: 3 / 10 dilution was used for administration.
Study BR1-021: 1 / 2 dilution was used for infusion administration.

Demographic and Baseline Characteristics

Table 19 demonstrates that the majority of the 2462 patients dosed with SonoVue in the Completed Cardiac Studies were male (71.8%) and white (86.4%). The mean age was 62.1 years (range: 19 to 96 years), the mean weight was 79.60 kg (range: 38.0 to 210.0 kg), and the mean height was 169.82 cm (range: 121.0 to 201.0 cm). For the 1361 patients for whom cardiac status had been recorded, the majority had no history of previous heart failure (1032/1361, 75.8%) and New York Heart Association (NYHA) classification I or II (850/1361, 62.5%).

Overall Incidence of Adverse Events

The overall incidence rate of adverse events reported in the Completed Cardiac Studies has decreased since the submission of the *Original NDA ISS* (18.9% versus 16.8%, respectively). The same is true for the incidence rate of related adverse events reported (9.1% versus 7.2%, respectively). The incidence of serious adverse events reported has not changed, and the incidence of patients discontinuing study participation due to an adverse event is relatively similar.

A summary of adverse events for the Completed Cardiac Studies is presented in **Table 20.** Of the 2462 patients who were administered SonoVue in the Completed Cardiac Studies, 414 (16.8%) experienced 663 adverse events. Study agent-related adverse events were reported by 178 patients (7.2%). The majority of events were mild and resolved without sequelae. Only 4 patients had adverse events that were considered severe in intensity (1 of which experienced hypertension and chills considered by the Investigator to be of 'unknown' relationship to study agent administration). Sixteen subjects (0.6%) had serious adverse events; 12 had events considered to be not related to study agent. Two patients (0.1%) died during the clinical trial: one died due to procedural complications during PCI and after a well-tolerated echocardiographic exam with SonoVue; the other died due to arterial rupture following ballooning of the left main artery. Neither death was considered to be related to the administration of SonoVue. One other patient died after suffering a myocardial infarction prior to the administration of SonoVue. Nineteen patients (0.8%) were discontinued due to adverse events, 10 of whom had events considered related to study agent.

Table 19
Demographic and Baseline Characteristics, Completed Cardiac Studies, SonoVue

Characteristic	*Original ISS* N = 1769	*Safety Update* N = 2462
Gender, n (%)		
Male	1272 (71.9)	1767 (71.8)
Female	497 (28.1)	695 (28.2)
Age (yrs)		
<65, n (%)	1024 (57.9)	1364 (55.4)
≥65, n (%)	745 (42.1)	1098 (44.6)
Mean (SD)	61.4 (11.10)	62.1 (10.91)
Range (Minimum, Maximum)	19, 96	19, 96
Race, n (%)		
White	1500 (84.8)	2128 (86.4)
Black	100 (5.7)	110 (4.5)
Hispanic	18 (1.0)	18 (0.7)
Asian	141 (8.0)	191 (7.8)
Other	10 (0.6)	15 (0.6)
Weight (kg)		
<75, n (%)	702 (39.7)	991 (40.3)
75 to 100, n (%)	878 (49.6)	1240 (50.4)
>100, n (%)	179 (10.1)	221 (9.0)
Unknown, n (%)	10 (0.6)	10 (0.4)
	(N=1759)	(N=2452)
Mean (SD)	80.23 (17.134)	79.60 (16.415)
Range (Minimum, Maximum)	40.0, 210.0	38.0, 210.0
Height (cm)	(N=1752)	(N=2445)
Mean (SD)	169.87 (9.584)	169.82 (9.357)
Range (Minimum, Maximum)	121.0, 201.0	121.0, 201.0
Location of Study, n (%)		
Europe	1111 (62.8)	1804 (73.3)
North America	568 (32.1)	568 (23.1)
China	90 (5.1)	90 (3.7)
NYHA Class, n (%)	(N=1361)	(N=1361)
I	536 (39.4)	536 (39.4)
II	314 (23.1)	314 (23.1)
III	43 (3.2)	43 (3.2)
IV (excluded by protocol)	0	
Not Collected	468 (34.4)	468 (34.4)
Previous Heart Failure, n (%)	(N=1361)	(N=1361)
Yes	328 (24.1)	328 (24.1)
No	1032 (75.8)	1032 (75.8)
Not Collected	1 (0.1)	1 (0.1)
Cumulative Volume of SonoVue, n (%)		
≤7.5 mL	1054 (59.6)	1097 (44.6)
>7.5 mL	712 (40.2)	1362 (55.3)
Unknown	3 (0.2)	3 (0.1)

Previous Heart Failure and NYHA classification were collected in Studies BR1-011, BR1-012, BR1-013, BR1-019A, BR1-019B, BR1-020, BR1-021, BR1-027, BR1-029, BR1-038, BR1-063, BR1-066, BR1-068, BR1-103, BR1-112, BR1-113, BR1-122, and BBG-001.

Table 20
Summary of Adverse Events, Completed Cardiac Studies, SonoVue

Category	*Original ISS* (N=1769)		*Safety Update* (N=2462)	
	Total	Related[a]	Total	Related[a]
No. (%) of Patients with at least 1 AE	335 (18.9)	161 (9.1)	414 (16.8)	178 (7.2)
No. (%) of Patients with at least 1 Serious AE	11 (0.6)	2 (0.1)	16 (0.6)	4 (0.2)
No. (%) of Patients who Discontinued due to AEs	12 (0.7)	5 (0.3)	19 (0.8)	10 (0.4)
No. (%) of Deaths	1 (0.1)[b]	0	2 (0.1)[b]	0
No of AEs[c]	558	261	663	288
No. (%) of Patients with at least 1 Non-serious AE by Intensity:[d]	327 (18.5)	159 (9.0)	401 (16.3)	174 (7.1)
Mild AEs	247 (14.0)	130 (7.3)	301 (12.2)	141 (5.7)
Moderate AEs	76 (4.3)	28 (1.6)	96 (3.9)	32 (1.3)
Severe AEs	4 (0.2)	1 (0.1)	4 (0.2)	1 (<0.1)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] One additional patient died prior to SonoVue administration; therefore, he is not included in the integrated safety database.
[c] Multiple occurrences of the same adverse event in a patient are counted individually.
[d] If a patient experienced more than 1 non-serious adverse event, the patient was counted only once at the maximum intensity.

Adverse Events by SOC and Preferred Term

A summary of the adverse event that occurred in >0.5% of the patients in the Completed Cardiac Studies is provided in **Table 21**. The most commonly reported adverse events (>0.5%) were headache (98 patients, 4.0%), chest pain (46 patients, 1.9%), nausea (37 patients, 1.5%), chest discomfort (27 patients, 1.1%), dyspnoea (16 patients, 0.6%), angina pectoris and hypotension (15 patients each, 0.6%), and dizziness (12 patients, 0.5%). The most commonly reported study agent-related adverse events (>0.5%) were headache (38 patients, 1.5%), nausea (23 patients, 0.9%), and chest discomfort (14 patients, 0.6%).

Serious Adverse Events

A listing of the serious adverse events that occurred in the Completed Cardiac Studies is provided in **Table 22**. Narrative summaries for each of the patients who experienced serious adverse events (including deaths) in the Completed Cardiac Studies as of September 30, 2011 were provided in the *Original NDA ISS*. Narrative summaries for each of the patients who experienced serious adverse events (including deaths) for the 2 Completed Cardiac Studies completed since the submission of the *Original NDA ISS* are provided in the updated document.

Table 21
Adverse Events by System Organ Class Reported in >0.5% of the Patients, All Completed Cardiac Studies, SonoVue

MedDRA System Organ Class / Preferred Term	*Original ISS* (N=1769)		*Safety Update* (N=2462)	
	Total	Related[a]	Total	Related[a]
No. (%) of patients with at least 1 AE	335 (18.9)	161 (9.1)	414 (16.8)	178 (7.2)
Cardiac Disorders				
Angina pectoris	11 (0.6)	1 (0.1)	15 (0.6)	2 (0.1)
Gastrointestinal Disorders				
Abdominal pain upper	8 (0.5)	2 (0.1)	10 (0.4)	4 (0.2)
Nausea	31 (1.8)	19 (1.1)	37 (1.5)	23 (0.9)
General Disorders/Administration Site Conditions				
Chest discomfort	26 (1.5)	13 (0.7)	27 (1.1)	14 (0.6)
Chest pain	31 (1.8)	8 (0.5)	46 (1.9)	10 (0.4)
Fatigue	8 (0.5)	3 (0.2)	8 (0.3)	3 (0.1)
Feeling hot	8 (0.5)	3 (0.2)	10 (0.4)	3 (0.1)
Investigations				
Blood glucose increased	11 (0.6)	8 (0.5)	11 (0.4)	8 (0.3)
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	10 (0.6)	4 (0.2)	10 (0.4)	4 (0.2)
Nervous System Disorders				
Dizziness	10 (0.6)	6 (0.3)	12 (0.5)	6 (0.2)
Dysgeusia	11 (0.6)	11 (0.6)	11 (0.4)	11 (0.4)
Headache	75 (4.2)	35 (2.0)	98 (4.0)	38 (1.5)
Tremor	8 (0.5)	0	8 (0.3)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	13 (0.7)	4 (0.2)	16 (0.6)	4 (0.2)
Vascular Disorders				
Hypotension	9 (0.5)	3 (0.2)	15 (0.6)	5 (0.2)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Table 22
Summary of Serious Adverse Events, Completed Cardiac Studies, SonoVue

Study No. / Site No. Patient No.	MedDRA System Organ Class / Preferred term	Onset Time / Duration (d:h:m)*	Relationship to Investigational Product	Action Taken§	Outcome#
BR1-011 / 09 0194	General Disorders and Administration Site Conditions / Chest Pain	00:15:29 / 00:02:00	Not related	Hosp	Rec
BR1-013 / 02 0201	Cardiac Disorders / Cardiac Failure Congestive	00:07:04 / 03:12:00	Not related	DrgTrt Hosp DiagTest	Rec
BR1-019A / 10 1007	General Disorders and Administration Site Conditions / Chest Pain	01:--:-- / < 1 day	Not related	DrgTrt Hosp	Rec
BR1-020 / 01 0140	Gastrointestinal Disorders/ Abdominal Pain Upper	00:06:10 / 00:01:00	Not related	DrgTrt Hosp	Rec
BR1-038 / 13 1312	General Disorders and Administration Site Conditions / Chest Pain	00:20:49 / 00:01:30	Not related	DrgTrt	Rec
	Investigations / Electrocardiogram ST Segment Elevated	00:20:49 / 01:--:--	Not related	DrgTrt	Rec
BR1-038 / 15 1509	Musculoskeletal and Connective Tissue Disorders / Exostosis	00:01:15 / --:--:--	Not related	DrgTrt Non-Drg Trt DiagTest	Rec
BR1-041 / 01 0014	Cardiac Disorders / Cardiogenic Shock	00:02:44 / 00:01:00	Not related	DrgTrt Non-Drg Trt Disc	Died
BR1-041 / 04 0063	Cardiac Disorders / Ventricular Rupture	04:03:28 / 01:--:--	Not related	Non-Drg Trt Hosp, Disc	Rec
BR1-066 / 14 1403	General Disorders and Administration Site Conditions / Chest Pain	00:00:47 / 00:00:10	Unknown[a]	Disc	Rec
	Investigations / Electrocardiogram ST Segment Elevation	00:00:47 / 00:00:10	Unknown[a]	Disc	Rec
	Vascular Disorders / Hypotension	00:00:47 / 00:00:10	Unknown[a]	Disc	Rec
BR1-103 / 09 0902	General Disorders and Administration Site Conditions / Chest Pain	01:02:23 / 02:21:30	Not related	Hosp	Rec
BBG-001 / 15 1504	Skin and Subcutaneous Tissue Disorders / Rash	00:00:01 / 00:00:20	Probable	Chg DrgTrt Hosp, Disc	Rec
	Nervous System Disorders / Syncope Vasovagal	00:00:08 / 00:00:02	Probable[b]	Chg DrgTrt Hosp, Disc	Rec
BR1-125 / 11 1101	Cardiac Disorders / Cardiac Arrest	00:00:15 / 00:00:57	Probable	Chg DrgTrt Hosp, Disc	Rec
BR1-125 / 16 1602	Vascular Disorders / Hypertension	00:00:17 / 00:00:21	Not related	DrgTrt Hosp, Disc	Rec

(continued)

Study No. / Site No. Patient No.	MedDRA System Organ Class / Preferred term	Onset Time / Duration (d:h:m)*	Relationship to Investigational Product	Action Taken§	Outcome#
BR1-125 / 33 3317	Cardiac Disorders / Ventricular Tachycardia	00:17:39 / 00:00:00	Not related	DrgTrt Hosp	Rec
BR1-125 / 33 3321	Vascular Disorders / Arterial Rupture	00:02:07 / 00:00:35	Not related	Non-Drg Trt Disc	Died
BRA/013 / 01 0107	Immune System Disorders / Anaphylactic Shock	00:00:05 / 00:00:30	Probable	Chg DrgTrt Hosp, Disc	Rec

[a] Relationship 'unknown' in clinical trial database, however, subsequent information received from the Investigator indicated that events were clearly related to ischemia triggered by dobutamine.

[b] Relationship 'probable' in clinical trial database, however, subsequent information received from the Investigator indicated that the vasovagal event was not directly related to SonoVue administration.

***d:h:m** = days:hours:minutes after first injection of investigational product (Day 1)

§ **Action taken**: None; Chg=Change in investigational product administration; Drgtrt=Drug treatment; Hosp=Hospitalization; DiagTest=Diagnostic or clinical test conducted; Disc=Discontinued from study; Non-Drg Trt = non-drug treatment (e.g., pacemaker).

#Outcome: Rec=Recovered without sequelae; Rec seq= Recovered with sequelae; Not rec=Not recovered; DiedTable data derived from *Original NDA ISS Data Listing 1.2* and *12-Month Safety Update Patient Data Listing 1*.

Adverse Events Resulting in Discontinuation

A summary of adverse events resulting in a patient discontinuing participation in the Completed Cardiac Studies is provided in **Table 23**.

Summary: Completed Cardiac Clinical Studies

Of the 2462 patients who received SonoVue in the Completed Cardiac Studies, 414 (16.8%) experienced 663 adverse events. Study agent-related adverse events were reported by 178 patients (7.2%). The majority of events were mild and resolved without sequelae. Only 4 patients had adverse events that were considered severe in intensity (1 of which experienced hypertension and chills considered by the Investigator to be of 'unknown' relationship to study agent administration). Sixteen subjects (0.6%) had serious adverse events; 12 of whom had events considered to be not related to study agent. One patient died after suffering a myocardial infarction prior to receiving SonoVue. Two patients (0.1%) died during the clinical trial: one died due to procedural complications during PCI and after a well-tolerated echocardiographic exam with SonoVue; the other died due to arterial rupture following ballooning of the left main artery. Neither death was considered to be related to the administration of SonoVue. Nineteen patients (0.8%) were discontinued due to adverse events, 10 of whom had events considered related to study agent.

Table 23
Summary of Adverse Events Resulting in Discontinuation, Completed Cardiac Studies, SonoVue

Study No.	Pt. No.	Adverse Event MedDRA Preferred Term	Relationship to Study Agent	Death	SAE	DC'd
BR1-020	0141	Fatigue	Not related			X
BR1-021	0015	Bradycardia	Possible			X
		Hypotension	Possible			X
BR1-041	0014	Cardiogenic shock	Not related	X	X	X
BR1-041	0063	Ventricular rupture	Not related		X	X
BR1-066	0101	Angina Unstable	Not related			X
BR1-066	0402	Anxiety	Not related			X
BR1-066	0604	Angina Pectoris	Not related			X
		Ventricular tachycardia	Not related			X
BR1-066	1403	Chest pain	Unknown*		X	X
		Electrocardiogram ST segment elevation	Unknown*		X	X
		Hypotension	Unknown*		X	X
* Relationship 'unknown' in clinical trial database, however, subsequent information received from the Investigator indicated that the events were clearly related to ischemia triggered by dobutamine.						
BR1-066	1501	Hot Flush	Possible			X
		Nausea	Possible			X
BR1-112	1018	Swollen tongue	Probable			X
BBG-001	0403	Headache	Not related			X
BBG-001	1504	Rash	Probable		X	X
		Presyncope	Probable*		X	X
BR1-125	0209	Injection site vesicles	Possible			X
BR1-125	1101	Cardiac arrest	Probable		X	X
BR1-125	1515	Hypotension	Possible			X
BR1-125	1602	Hypertension	Not related		X	X
BR1-125	3321	Arterial rupture	Not related	X	X	X
BR1-125	3601	Hypotension	Probable			X
BRA/013	0107	Anaphylactic shock	Probable		X	X
* Relationship 'probable' in clinical trial database, however, subsequent information received from the Investigator indicated that the vasovagal event was not directly related to SonoVue administration.						

7.4 Results – Completed Microvasculature Clinical Studies

As of the cut-off date for this Safety Update (December 31, 2012), 2 studies in the microvasculature population have been newly completed. Study BR1-127 was a Phase III multicenter, open-label, prospective study to assess the diagnostic accuracy of the use of SonoVue to guide prostate biopsies in comparison with the current practice of ultrasound-guided systematic biopsy in 282 patients (237 in the Main Part and 45 in the Optimization Part). Study BR1-129 was a Phase II explorative multicenter study with intra-patient comparison of SonoVue-enhanced ultrasonography of the liver versus CEMDCT/MRI in monitoring response to sorafenib therapy in 30 patients with advanced HCC. Both studies have been integrated into the pooled safety database and are, therefore, reported amongst the cumulative data provided below.

Patient Disposition

The disposition of all patients who participated in Completed Microvasculature Studies is provided in **Table 24**. A total of 3123 patients were enrolled in the studies, with 30 patients discontinuing prior to receiving SonoVue. Of the 3088 patients who received SonoVue, 2891 (93.6%) completed the studies, while 197 (6.4%) discontinued prematurely (3 for adverse events, 2 were lost to follow-up, 34 for withdrawal of consent, 2 for protocol violations, 153 for other reasons, and 3 for no reason specified).

Table 24
Disposition of Patients, Completed Microvasculature Studies, SonoVue

Number of Patients	*Original NDA ISS*	*Safety Update*
Enrolled (signed informed consent)	2811	3123
Discontinued Prior to Receiving Study Agent	19	30
Withdrawal of consent	6	6
Protocol violation	4	4
Other	9	20
Received Study Agent	2785*	3088*
Completed Study	2598 (93.3%)	2891 (93.6%)
Prematurely Discontinued	187 (6.7%)	197 (6.4%)
Adverse event	3 (0.1%)	3 (0.1%)
Lost to follow-up	2 (0.1%)	2 (0.1%)
Withdrawal of consent	34 (1.2%)	34 (1.1%)
Protocol violation	2 (0.1%)	2 (0.1%)
Other	143 (5.1%)	153 (5.0%)
No reason specified	3 (0.1%)	3 (0.1%)

* Percentages are based on the number of patients dosed.

Extent of Exposure to Study Agent

The exposure to study agent for the Completed Microvasculature Studies is provided in **Table 25**. For the 3058 patients dosed in the Microvasculature Studies, the mean total volume was 7.23 mL (range: 0.6 to 136.4 mL). All but 13 patients received doses ranging from <1 mL to 50 mL. Exposure for Study BR1-129 (N=30) was excluded from the pooled safety database as the study was designed with multiple visits that were 2 to 8 weeks apart which is very different from all other studies being summarized. All 30 subjects from this study received at least one injection of SonoVue.

Table 25
Exposure to Study Agent, Completed Microvasculature Studies, SonoVue

	Original NDA ISS	*Safety Update*
Total Volume SonoVue Administered (mL)		
N	2785	3058
Mean (SD)	7.24 (8.404)	7.23 (8.051)
Median	4.80	4.80
Range (Minimum, Maximum)	0.6, 136.4	0.6, 136.4
Cumulative Dose Categories		
≤1 mL	163 (5.9%)	163 (5.3%)
>1 to 5 mL	1541 (55.3%)	1669 (54.6%)
>5 mL to 10 mL	561 (20.1%)	704 (23.0%)
>10 mL to 50 mL	507 (18.2%)	509 (16.6%)
>50 mL	13 (0.5%)	13 (0.4%)

Only exposure to SonoVue 5 mg/mL is summarized. Study BR1-129 (N=30) is excluded as the study was designed with multiple visits that were 2 to 8 weeks apart which is very different from all other studies being summarized.

For summary exposure, undiluted volume was used. When diluted volume was administered, undiluted volume was computed for summary purposes.

Overall Incidence of Adverse Events

The overall incidence rate of adverse events reported in the Completed Microvasculature Studies has not changed since the submission of the *Original NDA ISS* (4.0% versus 4.3%, respectively). The same is true for the incidence rate of related adverse events reported (2.0% versus 2.2%, respectively) and the incidence of serious adverse events reported (0.2%) and patients discontinuing study participation due to an adverse event (0.1%). No death was reported in the newly completed studies.

A summary of the adverse events reported in the Completed Microvasculature Studies is provided in **Table 26**. Of the 3088 patients who were administered SonoVue in the Completed Microvasculature Studies, 132 patients (4.3%) experienced 188 adverse events, while study agent-related adverse events were reported for 67 patients (2.2%). Seven patients (0.2%) experienced serious adverse events, none of which was considered related to administration of study agent. One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings. Three patients (0.1%) died while participating in a clinical trial, and 1 patient died as a result of his underlying disease 2 weeks after completing a clinical trial (the occurrence of death was reported outside of the protocol-defined adverse event reporting window); all the deaths were considered unrelated to study agent administration.

Two patients (0.1%) discontinued as a result of an adverse event. All the adverse events were mild or moderate in intensity, with the exception of 1 event which was considered to be of severe intensity (body temperature increased).

Table 26
Summary of Adverse Events, Completed Microvasculature Studies, SonoVue

Category	*Original NDA ISS* (N=2785)		*Safety Update* (N=3088)	
	Total	Related[a]	Total	Related[a]
No. (%) of Patients with at least 1 AE	111 (4.0)	57 (2.0)	132 (4.3)	67 (2.2)
No. (%) of Patients with at least 1 Serious AE	6 (0.2)	0	7 (0.2)[b]	0
No. (%) of Patients who Discontinued due to AEs	2 (0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)
No. (%) of Deaths	3 (0.1)[c]	0	3 (0.1)[c]	0
No of AEs[d]	163	90	188	102
No. (%) of Patients with at least 1 Non-serious AE by Intensity:[e]	106 (3.8)	57 (2.0)	127 (4.1)	67 (2.2)
Mild AEs	91 (3.3)	52 (1.9)	110 (3.6)	61 (2.0)
Moderate AEs	14 (0.5)	5 (0.2)	16 (0.5)	6 (0.2)
Severe AEs	1 (<0.1)	0	1 (<0.1)	0

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] One additional patient, Patient No. 0610 of Study BR1-127, experienced a non-serious adverse event (prostatitis) during the study which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined adverse event reporting window.
[c] One additional patient, Patient No. 0816 of Study BR1-071, experienced serious adverse events (worsening of nausea and vomiting) during the study and died 2 weeks after completing the study.
[d] Multiple occurrences of the same adverse event in a patient are counted individually.
[e] If a patient experienced more than 1 non-serious adverse event, the patient was counted only once at the maximum intensity.

Adverse Events by SOC and Preferred Term

Adverse events occurring in >0.5% of the patients in the Completed Microvasculature Studies are provided in **Table 27.** The only adverse events occurring in >0.5% of the patients were abdominal pain (17 patients, 0.6%) and headache (14 patients, 0.5%). All other events occurred in <0.5% of the patients. No study agent-related adverse events were reported in >0.5% of the patients.

Table 27
Adverse Events by System Organ Class Reported in >0.5% of the Patients, Completed Microvasculature Studies, SonoVue

MedDRA System Organ Class / Preferred Term	*Original NDA ISS* Number (%) of Patients (N=2785)		*Safety Update* Number (%) of Patients (N=3088)	
	Total	Related[a]	Total	Related[a]
No. (%) of patients with at least 1 AE	111 (4.0)	57 (2.0)	132 (4.3)	67 (2.2)
Gastrointestinal Disorders				
Abdominal pain	16 (0.6)	2 (0.1)	17 (0.6)	2 (0.1)
Nervous System Disorders				
Headache	14 (0.5)	12 (0.4)	14 (0.5)	12 (0.4)

AE/s = Adverse Event/s.
[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Summary: Completed Microvasculature Clinical Studies

Of the 3088 patients who received SonoVue, 132 patients (4.3%) experienced 188 adverse events, 102 of which were considered to be study agent-related. Seven patients (0.2%) experienced serious adverse events, none of which was considered related to administration of SonoVue. One additional patient experienced a non-serious adverse event during study participation, which became serious when the patient was hospitalized due to worsening of symptoms outside of the protocol-defined reporting window (after the 24 hours post-dose monitoring period). The event was considered by the Investigator to be unrelated to the administration of SonoVue at both recordings. Three patients (0.1%) died during the study, and 1 additional patient died 2 weeks after the protocol-defined adverse event reporting window was closed; all 4 deaths were considered to be unrelated to study agent administration. Two patients (0.1%) discontinued as a result of an adverse event.

7.5 Results - Completed Observational Studies

SonoVue Study BR1-132 was a retrospective analysis investigating in-hospital mortality (within the same day as or the calendar day following performance of the echocardiography procedure) rate in 757 critically ill patients receiving echocardiography with the administration of (b) (4) in comparison with 3087 patients receiving echocardiography without contrast agent.

Patients hospitalized from 01 September 2001 to 31 May 2010 meeting the following inclusion criteria were enrolled in the study: male or female at least 18 years of age at the time the rest only echocardiography was performed; defined as critically ill according to at least one of the unstable cardiopulmonary conditions listed as the admitting diagnosis (i.e., worsening or clinically unstable heart failure [Class III/IV], recent acute coronary syndrome [ACS] or clinically unstable ischemic cardiac disease, recent coronary artery intervention within 7 days prior to the echocardiogram, severe rhythm disorders, other factors suggesting clinical instability, severe pulmonary hypertension [pulmonary artery pressure >90 mmHg], adult respiratory distress syndrome [ARDS], emphysema and/or chronic obstructive pulmonary disease, other [each site was to specify from the patient's medical history]); source medical records for primary clinical data were available and accessible; patients undergoing echocardiography with administration of SonoVue or without administration of any contrast agent; and echocardiography examination performed within 7 days from admission to the hospital for the unstable cardiopulmonary condition.

The results indicated that there was no statistically significant difference noted between critically ill patients who had undergone contrast echocardiography with SonoVue and critically ill patients who had undergone echocardiography without the use of a contrast agent with respect to in-hospital mortality (i.e., within the same day of echocardiography procedure and/or the following calendar day).

Univariate Analysis

Of the 3844 critically ill patients who met all of the eligible criteria for the study, 53 (1.38%) were included in the in-hospital mortality count as having died the same day as the echocardiography procedure and/or the following calendar day. Among the 53 patients, 48 (48/3087 patients, 1.55%) had undergone unenhanced echocardiography examination, and 5 (5/757, 0.66%) had undergone a SonoVue-enhanced echocardiography examination. There was no statistical difference between these 2 groups (p=0.067). The estimated crude odds ratio comparing the SonoVue Group with the Control Group was 0.42 with 95% CI 0.17 - 1.06.

Propensity Score Matched Analysis

The propensity score matching procedure had more than 80% of SonoVue patients (615/757 patients) who could be matched 1-to-1 with Control patients based on their closest baseline risk status. Covariates considered with best predictive power in the model for propensity score were: age, gender, admission to Emergency Room, Cardiac Care Unit, ARDS, coronary syndrome, pulmonary heart disorder, recent coronary artery intervention, severe rhythm disorder, worsening heart failure, anti-coagulant treatment, dyslipidemia, and muscular-skeletal disorder.

The overall similarity of the clinically important predictors indicates that the 2 groups were balanced after propensity score matching. Thus the analysis based on the matched subjects reduced potential confounding effect bias.

The propensity score matched analysis had comparable results to the univariate analysis. Of those 615 patients who had undergone unenhanced echocardiography, 10 (1.63%) died within the same day as the echocardiography procedure and/or the following calendar day. Of the 615 patients receiving SonoVue during echocardiogram, 5 (0.81%) died the same day as the echocardiography procedure and/or the following calendar day. There was no statistical difference between these 2 groups (p=0.068). The estimated adjusted odds ratio comparing the SonoVue Group with the Control Group was 0.30 with 95% CI 0.08 - 1.09.

Composite Endpoint of Mortality and Major Adverse Events

There was also no significant difference between the SonoVue Group versus the Control Group with respect to combined mortality and major adverse events in critically ill patients.

Comparison of Results for Retrospective Epidemiological Studies Using 3 Ultrasound Contrast Agents in Critically Ill Patients

Retrospective epidemiological studies in critically ill patients have also been conducted for the other 2 USCAs using a propensity-matched database. A comparison of the methods used amongst the 3 products is presented in **Table 28**. The results were similar

across all 3 studies: no increased risk of mortality was observed for patients undergoing echocardiography with a contrast agent compared with those undergoing unenhanced echocardiography.

Table 28
Comparison of Results for Retrospective Epidemiological Studies Using 3 USCAs in Critically Ill Patients

	SonoVue[15]		Definity[16]		Optison[16]	
Study Duration	1/9/01 – 31/5/10		1/1/02 – 15/6/08		1/1/03 – 1/11/05	
Data Source	Hospital records from sites in Europe		(b) (4) (billing database)		(b) (4) (billing database)	
Critically Ill Definition	ICD-9 CM for admitting illness (unstable cardio-pulmonary conditions)		Billing codes for ICU/CCU stay		ICD-9 CM for admitting illness	
Exclusion Criteria	No exclusion of stress echo		Stress echo patients excluded		No exclusion of stress echo	
Propensity Score Match	1:1		1:1		1:4 (CE vs non-contrast)	
All-Cause Mortality in Critically Ill Patients (Same Day or Next Day)	CE-Echo n/N (%)	Non-CE-Echo n/N (%)	CE-Echo n/N (%)	Non-CE-Echo n/N (%)	CE-Echo n/N (%)	Non-CE-Echo n/N (%)
	5/615 (0.8)	10/615 (1.6)	353/16199 (2.2)	443/16199 (2.7)	62/2883 (2.2)	217/11532 (1.9)
	OR=0.3 (0.08 - 1.09)		OR=0.8 (0.7 - 0.9)		OR=1.2 (0.9 - 1.6)	

CE-Echo=Contrast-enhanced echocardiography
OR = Contrast odds of mortality relative to non-contrast odds of mortality estimated with unconditional multivariate logistic regression models.

7.6 Results - Ongoing Clinical Trials

As of the data cut-off date for this document (final CTR available as of December 31, 2012), there were 2 ongoing Bracco-Sponsored Clinical Studies in approximately 677 subjects targeted to obtain efficacy and safety data on the use of SonoVue in subjects with focal liver disease for the characterization of focal liver lesions (Studies BR1-128 and BR1-130). Subject enrollment has been completed in both of these studies; however, study assessments (blinded reads) were still ongoing as of the data cut-off date for this update. The number of subjects exposed to SonoVue is displayed in **Table 29** for each study.

Table 29
Ongoing SonoVue Clinical Studies

Protocol Number	Title	No. of Subjects Exposed to SonoVue	
		Original ISS	*Safety Update*
Study Activity Ongoing as of December 31, 2012			
BR1-128	Characterization of Focal Liver Lesions with SonoVue-Enhanced Ultrasound Imaging: A Phase III, Intra-patient Comparative Study versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging / Clinical Data as Truth Standard	248 subjects (74* training, 174 efficacy)	337 subjects (74 training, 263 efficacy)
BR1-130	Characterization of Focal Liver Lesions with SonoVue-enhanced Ultrasound Imaging: A Phase III, Intra-patient Comparative Study versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging/Clinical Data as Truth Standard	119 subjects (52 training, 67 efficacy)	340 subjects (67 training, 273 efficacy)

* = Erroneously reported as 75 training cases dosed in the *Original NDA ISS*.

As of the data cut-off date of this Safety Update (December 31, 2012), 9 cases of serious adverse events were reported among the 677 subjects dosed in the 2 ongoing Bracco-Sponsored Clinical Studies. Of these 9 cases, 7 occurred before the submission of the NDA 203-684 and a description is presented in Appendix 3 of the *Original NDA ISS*, whereas 2 cases occurred after the NDA submission and are presented below.

- Case US-007303 (Study BR1-130, Patient No. 1625, SonoVue 2.4 mL): a 75-year-old male with a history of hypertension, high cholesterol, edema in bilateral legs, blood clots, arrhythmia, CAD, intermittent chest pain, insomnia, pacemaker placement, and an endoscopic biopsy of the pancreas to diagnose an Islet cell tumor, experienced extreme pain more than 24 hours after SonoVue-enhanced ultrasound-guided liver biopsy. The subject was admitted to the hospital for observation. A CT was performed which revealed a hemorrhage into the lower parenchyma of the right lobe and additional hemorrhage extending into the renal parenchyma (reported as "hemorrhage right liver lobe"). The subject was considered to be stable, and to have recovered from the hemorrhage (without surgery, other intervention or transfusion) and was released from the hospital 2 days later. The Investigator considered the event to be related to the liver biopsy, not the administration of SonoVue.

- Case FR-000791 (Study BR1-130, Patient No. 3003, SonoVue 2.4 mL), a 64-year-old female patient received SonoVue for an ultrasound to study focal liver lesions. The day after the procedure she presented with rectal hemorrhage (reported as "rectorrhagia") which led to hospitalization. The event recovered without treatment. The patient had history of diverticular sigmoiditis treated by sigmoidectomy, performed about a week before receiving SonoVue. The investigator considered the event to be not related to the administration of SonoVue, but a consequence of the previously performed surgery.

7.7 Results - Post-marketing Surveillance

Exposure

SonoVue is currently approved for intravenous use in 36 countries throughout the world and is marketed in 25 countries, indicated for use with echocardiography to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation, Doppler of macrovasculature, and Doppler of microvasculature.

SonoVue should be administered using a 5-mL single vial per investigation (doses: 2.0 mL for endocardial border detection or 2.4 mL for Doppler sonography of vessels, repeated once if necessary). An estimate of patient exposure is thus calculated on the basis of the number of single dose vials sold from April 1, 2001 to December 31, 2012. Denominators are estimated from sales statistics, with each unit sold representing a patient exposed to the agent.

During market use (April 1, 2001 through December 31, 2012), an estimated [redacted] patients have been exposed to SonoVue.

Adverse Reactions

Of the estimated [redacted] patients exposed to SonoVue during the market use of the product, adverse events for which both Reporter and Bracco causality assessments did not exclude causal relationship to the administration of SonoVue were spontaneously reported for 719 cases (reporting rate: [redacted]). A total of 322 cases (reporting rate of [redacted]) of the 719 cases were classified as serious and 397 non-serious (reporting rate of [redacted]). Adverse reactions (causality could not be ruled out by either the Reporter or Bracco) were reported in 702 cases (reporting rate: [redacted]), of which 307 were serious (reporting rate: [redacted]) and 395 were non-serious (reporting rate: [redacted]).

As demonstrated in **Table 30**, there is no notable difference in reporting rates for adverse reactions reported cumulatively for the *Original NDA ISS* and those reported for this Safety Update.

The total number of subjects with serious adverse events distributed in the last 11.5 years of marketing of SonoVue, with the exception of those events where both Reporter and Bracco excluded the causality relationship to the administration of SonoVue, is displayed in **Figure 1.** The SonoVue serious cases reporting rate per year through December 31, 2012 remains low (ranging from [redacted] to [redacted]) and stable across the last 11.5 years of Pharmacovigilance surveillance. This by month analysis excludes the first 6 months of marketing [April 1, 2001 to September 30, 2001], during which only [redacted] patients were exposed to SonoVue; in this period 2 adverse reaction case reports were received, 1 serious case and 1 non-serious case.

Table 30
Post-Marketing Surveillance: Comparison of Adverse Reactions by System Organ Class Spontaneously Reported from April 1, 2001 to September 30, 2011 for the *Original NDA ISS* and Reported from April 1, 2001 to December 31, 2012 for this Safety Update

Safety Update

MedDRA System Organ Class	*Original NDA ISS* (N= (b) (4))			*Safety Update* (N= (b) (4))		
	Number and Reporting Rate of Patients			Number and Reporting Rate of Patients		
	Serious	Non-Serious	Total	Serious	Non-Serious	Total
Total No. of Patients with Adverse Reactions	246 (b) (4)	204 (b) (4)	450 (b) (4)	307 (b) (4)	395 (b) (4)	702 (b) (4)
Cardiac disorders	64	9	73	77	17	94
Ear and labyrinth disorders	0	1	1	0	2	2
Eye disorders	4	6	10	4	11	15
Gastrointestinal disorders	8	51	59	9	71	80
General disorders and administration site conditions	24	121	145	32	279	311
Immune system disorders	146	19	165	176	26	202
Injury, poisoning and procedural complications	0	1	1	0	12	12
Investigations	32	11	43	40	19	59
Metabolism and nutrition disorders	0	0	0	1	0	1
Musculoskeletal and connective tissue disorders	4	8	12	4	12	16
Nervous system disorders	45	36	81	50	66	116
Pregnancy, puerperium and prenatal conditions	1	0	1	1	0	1
Psychiatric disorders	2	5	7	2	8	10
Renal and urinary disorders	4	3	7	4	5	9
Respiratory, thoracic and mediastinal disorders	42	16	58	53	25	78
Skin and subcutaneous tissue disorders	39	63	102	45	89	134
Surgical and medical procedures	2	11	13	3	19	22
Vascular disorders	45	18	63	61	26	87

NOTE: Patients are counted once for each system organ class; the same patient may be reported for more than one system organ class.
* = Estimated.
Table data derived from post-marketing surveillance database.

Figure 1
Reporting Rate of Serious Adverse Reactions in the Last 11.5 Years of SonoVue Marketing

The frequency distribution and reporting rate of all adverse events (with the exception of those events considered by both the Reporter and Bracco to be unrelated to the administration of SonoVue) from April 1, 2001 to December 31, 2012, sorted by MedDRA, version 15.1, SOC and PT, are presented in Table 31. The majority of serious reaction cases reported with (b) (4) were immune system disorders (176 cases), with the second most frequently reported serious events being cardiac system disorders (77 cases).

Table 31
Post-marketing Spontaneously Reported Adverse Reactions – Total Estimated Exposure to SonoVue: (b) (4) Patients from April 1, 2001 to December 31, 2012

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in (b) (4) Exposed Pts	Count	RR % in (b) (4) Exposed Pts	Count	RR % in (b) (4) Exposed Pts
Total No. of Subjects with Adverse Events		633	(b) (4)	813	(b) (4)	1,446	(b) (4)
Total No. of Adverse Events		307		395		702	
Cardiac disorders	Acute coronary syndrome	1		0		1	
	Acute myocardial infarction	2		0		2	
	Angina pectoris	2		0		2	
	Arrhythmia	1		0		1	
	Arteriospasm coronary	2		0		2	
	Atrioventricular block	1		0		1	
	Atrioventricular block complete	2		0		2	
	Atrioventricular block first degree	1		0		1	
	Atrioventricular block second degree	0		1		1	
	Bradycardia	22		1		23	
	Bundle branch block left	1		1		2	
	Cardiac arrest	15		0		15	
	Cardiac failure	1		0		1	
	Cardio-respiratory arrest	2		0		2	
	Cardio-respiratory distress	1		0		1	
	Cardiovascular disorder	1		0		1	
	Cyanosis	4		3		7	
	Myocardial infarction	3		0		3	
	Myocardial ischaemia	1		0		1	
	Palpitations	0		4		4	
	Prinzmetal angina	2		0		2	
	Sinus tachycardia	1		0		1	
	Supraventricular tachycardia	1		0		1	
	Tachycardia	16		5		21	
	Torsade de pointes	1		0		1	
	Ventricular fibrillation	2		0		2	
	Ventricular hypokinesia	1		0		1	
	Ventricular tachycardia	2		2		4	
	Sub-Total of Adverse Events	89		17		106	
	Sub-Total of Patients with AEs	77		17		94	
Ear and labyrinth disorders	Ear discomfort	0		1		1	
	Tinnitus	0		1		1	
	Sub-Total of Adverse Events	0		2		2	
	Sub-Total of Patients with AEs	0		2		2	
Eye disorders	Abnormal sensation in eye	0		1		1	
	Conjunctival hyperaemia	0		3		3	
	Conjunctivitis	0		1		1	
	Eyelid oedema	2		2		4	
	Ocular discomfort	0		1		1	
	Ocular hyperaemia	1		1		2	
	Vision blurred	0		5		5	
	Visual impairment	1		0		1	
	Sub-Total of Adverse Events	4		14		18	
	Sub-Total of Patients with AEs	4		11		15	

(continued)

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)
Gastrointestinal disorders	Abdominal discomfort	0	(b) (4)	2	(b) (4)	2	(b) (4)
	Abdominal pain	0		6		6	
	Abdominal pain upper	1		8		9	
	Aerophagia	0		1		1	
	Defaecation urgency	0		2		2	
	Dry mouth	0		3		3	
	Dysphagia	1		1		2	
	Eructation	0		1		1	
	Faecal incontinence	0		1		1	
	Lip oedema	0		1		1	
	Lip swelling	0		1		1	
	Nausea	4		39		43	
	Necrotising enterocolitis neonatal	1		0		1	
	Oral discomfort	1		0		1	
	Oral pain	0		1		1	
	Retching	0		4		4	
	Salivary hypersecretion	0		1		1	
	Swollen tongue	0		1		1	
	Tongue oedema	1		1		2	
	Vomiting	1		22		23	
	Vomiting projectile	0		1		1	
	Sub-Total of Adverse Events	10		97		107	
	Sub-Total of Patients with AEs	9		71		80	
General disorders and administration site conditions	Asthenia	1		2		3	
	Chest discomfort	6		6		12	
	Chest pain	6		5		11	
	Chills	1		11		12	
	Device occlusion	1		0		1	
	Discomfort	0		1		1	
	Drug effect decreased	0		103		103	
	Drug ineffective	1		118		119	
	Extravasation	0		1		1	
	Face oedema	2		0		2	
	Fatigue	0		2		2	
	Feeling abnormal	0		2		2	
	Feeling cold	0		1		1	
	Feeling hot	2		15		17	
	Foaming at mouth	1		0		1	
	General physical health deterioration	0		1		1	
	Infusion site phlebitis	0		1		1	
	Injection site erythema	0		1		1	
	Injection site haematoma	0		2		2	
	Injection site pain	0		2		2	
	Injection site rash	0		1		1	
	Injection site swelling	0		1		1	
	Localised oedema	1		0		1	
	Malaise	7		8		15	
	Oedema	1		1		2	
	Oedema peripheral	2		0		2	
	Pain	1		3		4	
	Product colour issue	0		30		30	

(continued)

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)
General disorders and administration site conditions (cont'd)	Product physical issue	0	(b) (4)	2	(b) (4)	2	(b) (4)
	Product quality issue	0		4		4	
	Product reconstitution issue	0		2		2	
	Product solubility abnormal	0		6		6	
	Puncture site pain	0		1		1	
	Pyrexia	2		3		5	
	Sudden cardiac death	1		0		1	
	Tenderness	1		0		1	
	Therapeutic response unexpected	0		1		1	
	Sub-Total of Adverse Events	37		337		374	
	Sub-Total of Patients with AEs	32		279		311	
Immune system disorders	Anaphylactic reaction	45		3		48	
	Anaphylactic shock	62		0		62	
	Anaphylactoid reaction	24		4		28	
	Anaphylactoid shock	3		0		3	
	Contrast media allergy	1		0		1	
	Drug hypersensitivity	1		1		2	
	Hypersensitivity	40		18		58	
	Type I hypersensitivity	1		0		1	
	Sub-Total of Adverse Events	177		26		203	
	Sub-Total of Patients with AEs	176		26		202	
Injury, poisoning and procedural complications	Contrast media reaction	0		1		1	
	Poor quality drug administered	0		10		10	
	Procedural pain	0		1		1	
	Sub-Total of Adverse Events	0		12		12	
	Sub-Total of Patients with AEs	0		12		12	
Investigations	Blood pressure decreased	22		12		34	
	Blood pressure immeasurable	3		0		3	
	Blood pressure increased	2		1		3	
	Body temperature decreased	0		1		1	
	Body temperature increased	1		2		3	
	Electrocardiogram ST segment elevation	8		1		9	
	Electrocardiogram ST-T segment abnormal	1		0		1	
	Electrocardiogram abnormal	1		0		1	
	Heart rate decreased	2		1		3	
	Heart rate increased	2		1		3	
	Oxygen saturation	0		1		1	
	Oxygen saturation decreased	7		1		8	
	Pulse abnormal	1		0		1	
	Pulse absent	2		0		2	
	Pulse pressure decreased	1		0		1	
	Respiratory rate decreased	0		1		1	
	Troponin increased	1		0		1	
	Sub-Total of Adverse Events	54		22		76	
	Sub-Total of Patients with AEs	40		19		59	
Metabolism and nutrition disorders	Acidosis	1		0		1	
	Sub-Total of Adverse Events	1		0		1	
	Sub-Total of Patients with AEs	1		0		1	

(continued)

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)
Musculoskeletal and connective tissue disorders	Arthralgia	1	(b) (4)	3	(b) (4)	4	(b) (4)
	Back pain	2		6		8	
	Groin pain	0		1		1	
	Joint stiffness	0		1		1	
	Joint swelling	0		1		1	
	Muscle spasms	1		0		1	
	Muscle twitching	0		1		1	
	Myalgia	0		1		1	
	Pain in extremity	1		0		1	
	Sub-Total of Adverse Events	5		14		19	
	Sub-Total of Patients with AEs	4		12		16	
Nervous system disorders	Akathisia	1		0		1	
	Altered state of consciousness	1		1		2	
	Burning sensation	1		3		4	
	Coma	1		0		1	
	Consciousness fluctuating	1		0		1	
	Convulsion	4		0		4	
	Depressed level of consciousness	4		1		5	
	Dizziness	2		11		13	
	Dysgeusia	0		12		12	
	Dyskinesia	0		1		1	
	Grand mal convulsion	1		0		1	
	Headache	1		8		9	
	Hyperaesthesia	0		1		1	
	Hypoaesthesia	2		4		6	
	Loss of consciousness	18		0		18	
	Ophthalmoplegic migraine	0		1		1	
	Paraesthesia	5		22		27	
	Phantom pain	0		1		1	
	Presyncope	8		4		12	
	Somnolence	1		1		2	
	Syncope	5		3		8	
	Transient ischaemic attack	3		0		3	
	Tremor	2		3		5	
	Unresponsive to stimuli	0		1		1	
	Sub-Total of Adverse Events	61		78		139	
	Sub-Total of Patients with AEs	50		66		116	
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1		0		1	
	Sub-Total of Adverse Events	1		0		1	
	Sub-Total of Patients with AEs	1		0		1	
Psychiatric disorders	Agitation	0		4		4	
	Confusional state	1		0		1	
	Insomnia	0		1		1	
	Mental status changes	0		1		1	
	Panic reaction	0		1		1	
	Restlessness	1		2		3	
	Sub-Total of Adverse Events	2		9		11	
	Sub-Total of Patients with AEs	2		8		10	

(continued)

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)
Renal and urinary disorders	Micturition urgency	0		1		1	
	Renal failure	1		0		1	
	Renal failure acute	2		0		2	
	Renal impairment	0		1		1	
	Urinary incontinence	1		3		4	
	Sub-Total of Adverse Events	4		5		9	
	Sub-Total of Patients with AEs	4		5		9	
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	2		0		2	
	Asthma	1		1		2	
	Bronchospasm	1		1		2	
	Choking sensation	1		0		1	
	Cough	6		5		11	
	Dry throat	0		1		1	
	Dysphonia	0		1		1	
	Dyspnoea	36		9		45	
	Epistaxis	0		1		1	
	Hyperventilation	0		2		2	
	Laryngeal oedema	2		0		2	
	Nasal congestion	0		1		1	
	Nasal discomfort	2		0		2	
	Oropharyngeal pain	1		0		1	
	Pharyngeal oedema	1		0		1	
	Respiratory arrest	5		0		5	
	Respiratory depression	1		0		1	
	Respiratory distress	1		0		1	
	Respiratory failure	1		0		1	
	Sneezing	0		1		1	
	Throat irritation	1		2		3	
	Throat tightness	3		2		5	
	Wheezing	1		1		2	
	Sub-Total of Adverse Events	66		28		94	
	Sub-Total of Patients with AEs	53		25		78	
Skin and subcutaneous tissue disorders	Cold sweat	3		10		13	
	Drug eruption	0		1		1	
	Erythema	13		20		33	
	Erythema multiforme	0		1		1	
	Generalised erythema	2		1		3	
	Hyperhidrosis	6		15		21	
	Lividity	0		1		1	
	Pain of skin	0		1		1	
	Pruritus	4		12		16	
	Pruritus generalised	0		3		3	
	Rash	8		15		23	
	Rash erythematous	2		1		3	
	Rash generalised	0		1		1	
	Rash maculo-papular	0		2		2	
	Rash papular	0		1		1	
	Rash pruritic	0		1		1	
	Skin discolouration	0		1		1	
	Skin reaction	0		3		3	
	Skin warm	0		1		1	
	Toxic skin eruption	1		0		1	

(continued)

MedDRA System Organ Class	Preferred Term	Number (%) of Events					
		Serious		Non-Serious		Total	
		Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)	Count	RR % in Exposed Pts (b) (4)
Skin and subcutaneous tissue disorders (cont'd)	Urticaria	12	(b) (4)	15	(b) (4)	27	(b) (4)
	Sub-Total of Adverse Events	51		106		157	
	Sub-Total of Patients with AEs	45		89		134	
Surgical and medical procedures	Off label use	3		19		22	
	Sub-Total of Adverse Events	3		19		22	
	Sub-Total of Patients with AEs	3		19		22	
Vascular disorders	Circulatory collapse	5		0		5	
	Flushing	7		14		21	
	Hot flush	1		1		2	
	Hypertension	2		0		2	
	Hypotension	47		4		51	
	Pallor	1		6		7	
	Peripheral coldness	0		1		1	
	Shock	5		0		5	
	Vasodilatation	0		1		1	
	Sub-Total of Adverse Events	68		27		95	
	Sub-Total of Patients with AEs	61		26		87	

The overall reporting rate of allergic-like reactions during SonoVue market use based on the Reporter's diagnosis, is <0.01% (1 in 10,000). Allergic-like reactions included the terms anaphylactic reaction/shock, anaphylactoid reaction/shock and hypersensitivity.

Serious Cases with Allergy-like Reactions

No significant difference was seen in the number of serious cases with allergy-like reactions reported in the 15 months following the data cut-off date of the *Original NDA ISS* (September 30, 2011).

Of the 307 patients reporting serious reactions, 176 (57%) were diagnosed by the initial reporter as allergy-like (e.g., anaphylactic/anaphylactoid reaction, anaphylactic shock, hypersensitivity) reactions. According to a systematic review of the serious adverse drug reaction (ADR) reports performed by Bracco, an additional 53 ADR cases should be medically classified as allergy-like events.

Therefore, a total of 229 out of 307 patients with serious ADR had an allergy-like reaction and the overall incidence of serious allergic reactions is estimated to be in the order of 1:10,000 exposed to SonoVue as of December 31, 2012. In most cases allergy-like events presented an onset within a few minutes from the injection of the product. In 53 of the 229 serious allergy-like reactions, hypotension (preferred terms: hypotension, blood pressure decrease, blood pressure immeasurable, syncope, presyncope, circulatory collapse, and pulse pressure decrease) was reported at the onset of the allergy-like reaction. The severity of hypotension could range from a reduction of a few millimetres of mercury in systolic blood pressure and diastolic blood pressure to non-measurable levels.

Serious Cardiac Reactions

No significant difference was seen in the number of serious cardiac cases reported in the 15 months following the data cut-off date of the *Original NDA ISS* (September 30, 2011). A total of 94 patients experienced 106 cardiac-related adverse drug reactions during the postmarketing surveillance period of April 1, 2001 to December 31, 2012. Of the 94 patients, 77 ((b) (4) of exposed patients) experienced serious cardiac-related adverse reactions. After a medical review of all PTs (preferred terms) in the remaining serious cases, an additional 41 ADR cases (preferred terms: blood pressure decreased, blood pressure immeasurable, electrocardiogram ST segment elevation, heart rate decreased, pulse abnormal pulse absent, pulse pressure decreased, hypotension, shock, and circulatory collapse) were included in the count of serious cardiac related cases for a total of 118 patients. Seventy-one (71) of these cases (60.2%) were associated with allergy-like/anaphylactoid reactions.

Post-marketing Surveillance Death Cases

Since the submission of the *Original NDA ISS*, 2 new cases with fatal outcome have been received by the Sponsor for a total of 11 deaths ((b) (4)) reported during post-marketing use of SonoVue (since the launch of the product in 2001). The association of the deaths with SonoVue administration could not be ruled out in 9 of the 11 cases; there was no relation to SonoVue reported for the remaining 2 cases.

In addition to these 11 patients, 2 other patients experienced unrelated serious adverse events after the administration of SonoVue and subsequently died, and 1 other patient who experienced a serious adverse event of anaphylactoid shock with recovered / resolved outcome, considered to be related to the administration of SonoVue, and subsequently died almost 7 weeks later due to their underlying cardiac disease. Narratives for 10 of these 14 patients were provided in the *Original NDA ISS*; the 4 remaining cases are provided below.

Report Describing Case with Recovered / Resolved Outcome

DE-000911

This patient was a 66-year-old male with a medical history of dilated cardiomyopathy, coronary heart disease, hypertension, lipid metabolism disorder, diabetes mellitus and heart failure (NYHA grade II), without known allergies, concomitantly treated with beta blockers, angiotensin-converting-enzyme inhibitors, statins, clopidogrel, aspirin acid, torasemide, insulin, metformin and allopurinol, underwent an ultrasound procedure for evaluation of cardiac failure with intravenous SonoVue (2 mL). Two minutes later, the patient experienced an anaplylactic shock, characterized by hypotension, tachycardia, loss of consciousness and circulatory failure. The patient was intubated and resuscitation efforts commenced for 15 minutes. He received 500 mg of prednisolone, 1 ampule of dimetindene maleate, epinephrine, norepinephrine and isotonic solutions. The patient was admitted to the intensive care unit where he remained for 2 weeks. He had completely

recovered from the event when he was transferred to a rehabilitation facility 15 days later. The reporter assessed the anaphylactic shock as certainly related to the administration of SonoVue. The patient died almost 3 weeks later due to progression of his underlying cardiac disease.

Report Describing Case with Fatal Outcome Considered to be of No Association with the Administration of SonoVue

CN-000321

This patient was a 49-year-old female patient underwent a contrast-enhanced abdominal ultrasound due to a "huge ovarian cancer" to detect the uterus and two appendices. A previous MRI showed multiple abdominal tumors and a pelvic solid-cystic mass. Approximately 10 to 40 minutes after the administration of 2.1 mL SonoVue, the patient felt discomfort and then experienced chest distress, dyspnea, followed by loss of consciousness and a sudden decrease in blood pressure (within the range of 80-110/20-50 mmHg) which was characterized as “shock” by the reporter. Resuscitation was started immediately and lasted 2 hours; the patient was treated with unspecified doses of adrenaline and dexae methasone. 30 minutes after resuscitation, the patient regained consciousness and was able to talk for several minutes. Systolic blood pressure “returned to 50 mmHg”. Several minutes later, the patient’s condition worsened and she died. It was reported that the patient’s death was due to pulmonary embolism caused by the cancer, which was confirmed by the autopsy report.

Report Describing Case with Unknown Outcome

IT-002146

This patient was a 54-year-old male patient received SonoVue for a contrast-enhanced examination in the context of an investigator’s initiated study protocol, following a Thoracic Endovascular Aortic Repair (TEVAR) procedure of descending thoracic aorta disease in order to detect early endoleaks. According to the protocol, a single 2 mL bolus of contrast agent, dissolved in 0.9% saline solution, was injected, followed by flushing with an injection of a 5 mL bolus of saline solution. During the night after surgery, 12 hours after SonoVue administration, the patient died as a result of post-operative complications, i.e., bleeding in the left carotid artery together with acute respiratory insufficiency. The investigator assessed the occurrence as not related to SonoVue administration.

Report Describing Case with Fatal Outcome Where the Association with the Administration of SonoVue Could Not Be Ruled Out

NL-000056

This patient was a 72-year-old male patient, with history of NSTEMI with stent placement approximately 3 months prior to examination, who underwent a pharmaceutical stress echocardiogram with dobutamine for assessment of ischemia. Patient received 1 mL intravenous SonoVue and, 30 second later, 5 mcg/kg/min intravenous dobutamine. After the administration of SonoVue and within 1.5 minutes

dobutamine infusion, the patient reported feeling a tingling sensation and needed to urinate. The patient denied any other symptoms such as wheezing, itch or throat tightness, and no skin abnormalities were noticed. Two minutes after the injection of SonoVue and 1.5 minutes after dobutamine infusion pump was started, the patient went into an anaphylactic shock. He was treated with reanimation, fluid NaCl 0.9% (normal saline), 100 mg hydrocortisone, 1 mg Tavegyl (clemastine) and 1 mg adrenaline (epinephrine). His blood pressure dropped (no values available) and shortly became immeasurable. The patient had tachycardia and then developed bradycardia (no values available). ECG showed diffuse ST elevation on D2-D3, aVR-aVL, V4-V6. An ultrasound performed 20 minutes after SonoVue administration showed transmural ischemia. There were still no muco-cutaneous or respiratory signs and symptoms and the patient initially was pale and conscious, but later lost consciousness. A diagnosis of anaphylactic shock was made by the cardiologist. Following the previously described treatment and extensive resuscitation maneuvers, the patient recovered consciousness; however, blood pressure remained not measurable. One hour after SonoVue and dobutamine administration, the patient went into cardiac arrest and died the same day. No autopsy was performed as denied by the patient's family.

Post-marketing Surveillance Since the Cut-off Date of December 31, 2012

Since the data cut-off of this Safety Update, a RFI was received from the Division on April 24, 2013 regarding Bracco's March 29, 2013 submission of Safety Report Identification GB-BRACCO-000695 to IND 46,958. Provided below is the narrative for this case.

GB-000695 (case was received after the December 31, 2012 cut-off date)
This patient was a 62-year-old patient with coronary artery disease underwent resting part of dobutamine stress echocardiography enhanced with SonoVue (2.1 mL) on (b) (6) Patient had a massive acute myocardial infarction, involving the anterior wall and the interventricular septum, in September 2012. He underwent PTCA (percutaneous coronary angiography and revascularization with placement of a stent in the left descending coronary artery) after the heart attack. The reporter initially indicated that the patient was on treatment with beta-blockers and dual antiplatelet therapy (aspirin and clopidogrel), but those drugs were not detected by the post-mortem drug laboratory investigations. Instead, the patient was on a diuretic (eplerenone) and amiodarone (antiarrhythmic), probably because of heart failure. About 2 minutes after SonoVue injection, patient experienced malaise and tingling in arm and back, suspected by the reporter to be an anaphylactoid reaction. Hydrocortisone and chlorpheniramine were administered but, approx. 1 minute later, he experienced a grand mal seizure and became unresponsive. Only slight increase in pulse (73 to 99 bpm) and decrease in BP (164/90 to 121/96) occurred. He then went into cardiac arrest, manifested with pulseless electrical activity and ventricular fibrillation, from which he could not be resuscitated, despite adrenaline, cardiopulmonary resuscitation and electric shocks for about 40 minutes. The patient died approx. 60 minutes from onset of symptoms. Baseline echo revealed segmental wall motion with a reserved left ventricular ejection fraction. The reporting

physician initially stated that the patient was likely to have had an intracranial event probably a bleed which he assessed as most likely unrelated to SonoVue.

An autopsy was performed on the patient and showed biventricular hypertrophy and dilatation, a stent in the left descending coronary artery with significant atheroma and 90% luminal narrowing, an extensive old myocardial infarction, involving the anterior wall and the interventricular septum, pulmonary edema, liver congestion and elevated serum mast cell tryptase levels (76.2 mg/L). Pulmonary embolism, right-to-left shunt or brain damage were excluded. After consultation with an immunologist, the final cause of death was indicated as anaphylactic shock reaction to the administration of SonoVue in a patient with ischemic heart disease.

Table 32 displays the incidence of reported serious adverse events and cases of death reported for the *Original NDA Submission*, the *4-Month Safety Update*, the time between the cut-off date of the *4-Month Safety Update* until the date the RFI was received, in addition to the cumulative data.

Table 32
Comparison of Safety Data from Post-Marketing Surveillance for SonoVue

	Original NDA Submission	4-Month Safety Update	Data Available as of Receipt of RFI	Cumulative Data Available as of Receipt of RFI
Timeframe	April 1, 2001 to September 30, 2011	October 1, 2011 to January 31, 2012 (4 months)	February 1, 2012 to April 24, 2013 (14.5 months)	April 1, 2001 to April 24, 2013 (12 years)
Estimated Exposure	(b) (4)			
Serious Adverse Events [a]	251 (b) (4)	19 (b) (4)	65 (b) (4)	335 (b) (4)
Serious Adverse Reactions [b]	246	19	61	326
Fatal Cases [c]	9 [d]	0[e]	3 [f]	12 [d,e,f]
Fatal Cases Where Association with SonoVue Could Not be Ruled Out[g]	6[h]	0	1	7[h]

a Serious adverse events (including cases with fatal outcome) regardless of association with the administration of SonoVue.
b Serious adverse events (including cases with fatal outcome) for which association with the administration of SonoVue could not be ruled out.
c All cases of fatal outcome, regardless of Reporter and Bracco causality assessment.
d One additional case of death was reported for a patient who experienced serious adverse events of ventricular fibrillation and cardiac arrest during a stress echocardiogram with unknown outcome and subsequently died 19 days after the administration of SonoVue. Both events were considered to be unrelated to the administration of SonoVue.
e One additional case of death was reported for a patient who experienced anaphylactic shock, considered to be related to SonoVue administration, and recovered completely after 28 days. Three weeks after the recovery, the patient died due to cardiac disease.
f One additional case of death was reported for a patient who experienced serious adverse events of bleeding in the left carotid artery and acute respiratory insufficiency 12 hours after the administration of SonoVue; both events were considered to be unrelated.
g Count based on Bracco's medical assessment of each fatal case as requested in the RFI of April 24, 2013.
h Includes 3 cases with causality of "unassessable".

Conclusions from Post-Marketing Surveillance

In summary, data from post-marketing surveillance database showed:
• the adverse reactions reported for SonoVue were, in general, non-serious, transient, and resolved spontaneously without residual effects;

• serious allergy-like reactions may unpredictably and rarely occur after SonoVue administration, and do not appear to differ from that of many contrast agents. While the reporting rate for serious adverse events is very low, fatalities have followed administration.
• no significant change in the safety profile of SonoVue has been demonstrated since the submission of the *Original NDA ISS*.

7.8 Results - Safety Data Reported in the Literature

For the *Original NDA ISS,* a literature search was performed on September 30, 2011 to provide supportive evidence of the safety of intravenous SonoVue administration during echocardiography and non-cardiac ultrasound studies. A total of 763 references were identified in the PubMed search result, among which 87 publications met the inclusion criteria and were summarized. The same search criteria were used for the 4-month safety update, and again for this update with the cut-off date of December 31, 2012 to identify any newly published literature. The new search yielded 37 additional articles, 11 of which were considered to be relevant. Two of the published articles demonstrated the use of SonoVue in the Cardiac Population and 9 were included among the Non-Cardiac Population.

Therefore, the total number of patients included in the 98 publications that reported safety information is 44,865, of whom, 13,498 underwent echocardiography examinations for cardiac indications reported in 22 publications and 31,097 underwent ultrasound examinations for non-cardiac indications reported in 76 publications. Overall, from 18 of the 22 published reports (referenced in the *Original NDA ISS* and Safety Update) 2830 cardiac patients receiving SonoVue during rest and stress echocardiography, the rate of adverse events was 0.35%. In the remaining 4 publications, studies of SonoVue and other contrast agents did not define the incidence rate of adverse event for each contrast agent.

As of April 24, 2013, a total of 12 deaths occurred during spontaneous reporting since the launch of the product in 2001 ((b) (4)). As requested in the April 24, 2013 RFI, Bracco performed a medical assessment of each of these cases and concluded that the association with SonoVue administration could not be ruled out in only 7 cases of fatal outcome, 3 of which were actually considered to be "unassessable". Two further reports of patients who experienced unrelated serious adverse events with unknown outcome and subsequently died after the injection of SonoVue have been received, in addition to another case where a patient experienced anaphylactic shock, considered to be possibly related to the administration of SonoVue, who completely recovered after 28 days, and then died due to his underlying cardiac disease 3 weeks after recovering from the anaphylactic shock.

7.9 Special Safety Concerns

Based on the reviewed data from the recently conducted hemodynamic study (BR1-133), 3 of the 36 patients dosed in the Special Patient Population study collectively reported 4 non-serious adverse events. The relationship to the administration of SonoVue could not be ruled out by the Investigator for 2 of the 4 events (both were considered to be of unknown relation to the administration of SonoVue). No serious adverse events or deaths were reported, and no patient discontinued the study due to an adverse event.

8. Medical Officer's Summary Safety Conclusions

The reviewed data within this document, based on the completed and ongoing clinical trials, cardiac, microvascular and observational studies, post-marketing surveillance and literature search, demonstrated that there is little to no change to the safety profile of SonoVue between the filing of the *Original NDA ISS* and the submission of this Safety Update.

In clinical trials, the overall incidence of adverse events was relatively low (10.7% overall, 5.2% study agent-related) in subjects receiving SonoVue. The most frequently reported adverse events were headache (2.1%), nausea (0.9%), chest pain (0.8%), and chest discomfort (0.5%). All other adverse events occurred at a frequency of <0.5%. Most adverse events were mild and resolved spontaneously within a short time without sequelae. Among adverse events, 0.4% (27) of patients reported at least 1 serious adverse event and 0.1% (5) were considered to be of some relationship to the administration of SonoVue (probable, possible, or unlikely).

A total of 10 deaths were reported from all completed clinical studies during the Safety Review. Each of these deaths was considered to be unrelated to study agent by both the Investigators and Bracco. This reviewer confirmed that each death was unrelated to study agent. No drug-related deaths were reported within Bracco sponsored trials.

The retrospective study (Study BR1-132) showed the agent does not seem to increase the risk of serious or fatal events in the critically ill population undergoing echocardiography. Of the 615 propensity score-matched patients who had undergone unenhanced echocardiography, 10 (1.63%) died within the same day as the echocardiography procedure and/or the following calendar day. Of the 615 patients receiving SonoVue during echocardiogram, 5 (0.81%) died the same day as the echocardiography procedure and/or the following calendar day. There was no statistical difference between these 2 groups (p=0.068). The estimated adjusted odds ratio comparing the SonoVue Group with the Control Group was 0.30 with 95% CI 0.08 - 1.09.

Experience from post-marketing surveillance of the estimated (b) (4) patients exposed to SonoVue from April 1, 2001 through April 24, 2013 during the market use of this product shows a total of 335 cases of serious adverse reactions considered to be of some relationship to the administration of SonoVue (reporting rate: (b) (4)).

During the post-marketing surveillance, a total of 14 fatal cases have been reported. Narratives for 9 of these patients were provided in the *Original NDA ISS (*summarized in Section 3 of this document). Narratives were provided for 4 deaths in the current Safety Update and for an additional case received since the cut-off date of Dec. 31, 2012 (Section 7.8).

This medical reviewer assessed the causality of each death as relates to the administration of SonoVue. **Table 33** summarizes the assessments of causality for all deaths reported during the post-marketing surveillance as either an **Unrelated, Possible or Probable** relationship to SonoVue administration. Five of the 14 deaths, those assessed as probably related to SonoVue administration, fit a similar clinical pattern i.e., anaphylactic reaction/shock, anaphylactoid reaction/shock and hypersensitivity shortly following administration of SonoVue.

Table 33 Assessment of Causality of Deaths Associated with SonoVue Administration

		Post-Marketing Surveillance Time Period			
		Original NDA ISS	**4 Month Safety Update**	**Post Cut-Off**	**Total**
Deaths (n)		**9**	**4**	**1**	**14**
Causality Assessment	**Unrelated**	**2**	**3**	**0**	**5**
	Possible	**4**	**0**	**0**	**4**
	Probable	**3**	**1**	**1**	**5**

Serious hypersensitivity reactions were observed in approx. 1 in 10,000 exposures. In about half of the hypersensitivity cases, symptoms in other SOCs were also reported, among which events of cardiac, vascular, respiratory, neurology and skin/subcutaneous tissue were the most frequently reported, consistent with the typical signs and symptoms of serious hypersensitivity reactions with multi-organ system involvement.

As already reported in the *Original NDA ISS,* the observed pattern of serious hypersensitivity reactions is similar to that reported for anaphylactic or anaphylactoid reactions to other intravascular contrast or imaging agents. In most of these cases of apparent hypersensitivity, the initial signs or symptoms started within 5 minutes from the injection of SonoVue. The initial symptoms ranged from mild to severe and could rapidly progress to medically important or life-threatening events.

SonoVue has been shown to be well tolerated among cardiac and non-cardiac patients, with minimal additional risk to patients. Overall, SonoVue demonstrated a positive benefit-to-risk ratio, indicating a usefulness for patients with suboptimal echocardiography.

Serious adverse events and fatalities, typically cardiopulmonary and/or anaphylactoid in nature, can be rarely observed with SonoVue. The majority of these events were observed within 30 minutes of contrast administration. The seriousness and time of the fatalities and adverse events underscore the importance of proper warnings, close patient observation, and the need for prompt availability of life-supporting equipment and trained personnel.,

Whereas administration of SonoVue, similar to other intravenously administered contrast agents, has the potential to be associated with the immediate onset of serious life-threatening events, physicians administering these agents may need guidance in management of these SAEs involving the immune, cardiac, vascular, respiratory, and nervous systems. As demonstrated in the case reports of deaths provided, when confronted with such emergencies in patients with known coronary artery disease, clinicians have had difficulty distinguishing cardiac from anaphylactic causation, thus impeding timely initiation of proper therapeutic measures. Availability of this information may be beneficial in providing guidance to assist clinicians when suddenly faced with such medical emergencies.

9. Review of Pediatric Development Plan

9.1 Overview of the Disease in the Pediatric Population

In the last 15 years intravenous contrast echocardiography has been demonstrated to be a useful tool in optimizing endocardial border delineation (EBD) in adult patients with poor transthoracic image quality. Over the same time period, echocardiography has become the primary imaging tool in the diagnosis and assessment of congenital and acquired heart disease in children and adolescents. No ultrasound imaging agent is approved by the Food and Drug Administration (FDA) for use during pediatric echocardiography because the safety and efficacy of ultrasound contrast has not been established in pediatric patients.

Poor echocardiographic windows, a common challenge in adults, might also affect the quality of examinations in pediatric patients due to adipose tissue, skeletal abnormalities such as pectus excavatum or carinatum, pulmonary disease, scar tissue in postoperative patients, or during stress examinations. Tissue harmonic imaging has been shown to improve visualization of the cardiac structures over fundamental imaging in children with poor echocardiographic windows without the need to use ultrasound contrast. This might have been the reason why, despite 15 years of clinical use, reported experience with ultrasound contrast agents in pediatric patients has been limited to two small-scale, single-center studies.

Zilberman et al. (2003) conducted a pilot study to evaluate the feasibility of intravenous

transpulmonary contrast (Optison, GE Healthcare) in pediatric patients and to compare the quality of endocardial visualization by harmonic imaging alone with harmonic echocardiography with contrast. All patients with known or suspected coronary abnormalities referred for stress echocardiography by their primary cardiologists were included. It took 14 months to enroll patients (age: 8 months to 19 years; mean: 9.3 years). These were patients with acquired (heart transplantation, Kawasaki disease), or congenital (status post arterial switch procedure for D-transposition of the great arteries, aortic stenosis, or coronary fistula) cardiac diseases and patients with chest pain. Patients with intracardiac shunt lesions were excluded to prevent possible cerebral vascular accidents associated with contrast administration. All patients underwent dobutamine (19 patients) or exercise (3 patients) stress echocardiography. None had intracardiac shunting. Each patient underwent both harmonic imaging alone and harmonic imaging with contrast administration at peak stress. Of note, use of contrast during stress echocardiographic examinations is not approved in the United States even for adult patients. Oxygen saturation, heart rate, and blood pressure were monitored. Endocardial delineation was evaluated by qualitative grading of 22 endomyocardial regional segments in each patient. Contrast images were graded by an echocardiographer who was blinded to the scores previously assigned to harmonic echocardiography images. There were no changes in oxygen saturation, heart rate, or blood pressure during or after contrast administration. Use of contrast significantly improved endocardial border visualization in 11 of 22 segments ($P < 0.05$), particularly lateral, apical, and anterior left ventricular wall segments.

McMahon et al. (2005) performed a study to determine the safety and efficacy of intravenous contrast echocardiography in children attending a tertiary cardiac center. This was a prospective study to evaluate the use of Optison in children with severely limited transthoracic echocardiographic windows. In 31 months, 20 children (median age, 15 years; range, 9-18) were recruited and underwent fundamental imaging, harmonic imaging, and harmonic imaging with Optison. EBD was determined based on a visual qualitative scoring system (0, none: 4, excellent). Endocardial border delineation was better with unenhanced harmonic imaging vs. fundamental imaging; however, EBD was further significantly improved in all patients using contrast echocardiography. Improved EBD was most marked in the apical and left ventricular free wall regions. No patients suffered adverse hemodynamic effects, changes in taste, or flushing episodes. Three patients experienced transient headaches.

No studies have ever been reported regarding the use of ultrasound contrast agents during rest echocardiography inpatients below 9 years of age. No studies were ever reported with the use of (b) (4) in pediatric echocardiography, despite the availability of the agent in the European Union and other countries since 2001.

(b) (4)

[redacted] (b) (4)

The FDA acknowledged that published literature suggested the occurrence of suboptimal transthoracic echocardiography is less frequent in pediatric patients than in adults; however, FDA stated concern that some pediatric patients could benefit from the use of ultrasound contrast agents, especially older pediatric patients with suboptimal echocardiograms due to obesity or chest structural deformities, as exemplified by the single-center report by McMahon et al. According to FDA, this single center experience did not support [redacted] (b) (4)

To comply with the request received from FDA, Bracco now plans to study the safety and efficacy of SonoVue in children 9 to 17 years of age with suboptimal images undergoing rest transthoracic echocardiography with harmonic imaging. Bracco is requesting a partial waiver of pediatric studies only in the age group of below 9 years of age based on the absence of clinical experience of contrast use in rest echocardiography in that age group, implying absent or extremely limited clinical need of the intended indication in patients aged between 1 and 8 years. This was confirmed by a survey conducted from 10 cardiologists with experience in pediatric cardiology from 10 different cardiovascular centers in the United States having well-established departments of pediatric cardiology. The results of this survey showed that 8 of the 10 centers surveyed do not use ultrasound contrast in their pediatric cardiac centers. One center uses it in rare instances for non-cardiac use in muscular dystrophy in patients aged 14-20 years and one center uses it occasionally for myocardial perfusion imaging, but not for EBD, during stress examination in patients aged 15-20 years with Kawasaki, a very rare disease.

9.2 Overview of the Drug Product

[redacted] (b) (4) is for diagnostic use only with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved delineation between blood and surrounding tissues. This medical imaging agent should only be used in patients where echocardiography without contrast enhancement is inconclusive. [redacted] (b) (4) was first approved in 15 countries of the European Union on 26 March 2001. It is now approved for use in echocardiographic examinations of adult patients with suboptimal images in a total of 36 countries worldwide.

9.3 Sponsor's Request for Product Specific Waiver(s)

Per the Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act*, published in September 2005, Bracco Diagnostics Inc. is submitting a request for a partial waiver for children less than 9 years of age. Reference is made to the FDA's Complete Response letter to their pending application for SonoVue received October 19,

2012. Further reference is made to pediatric studies required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), as all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

The FDA acknowledged that published literature suggested the occurrence of suboptimal transthoracic echocardiography is less frequent in pediatric patients than in adults; however, FDA stated concern that some pediatric patients could benefit from the use of ultrasound contrast agents, especially older pediatric patients with suboptimal echocardiograms due to obesity or chest structural deformities, as exemplified by the single-center McMahon et al. report that described 20 pediatric patients with suboptimal echocardiograms who had improved images with intravenous contrast. This single center experience also did not support (b) (4)

Bracco is now requesting a Partial Waiver of pediatric studies only in the age group of below 9 years of age based on the limited applicability to that specific age group population of the intended indication in patients with suboptimal echocardiograms. There is no published literature of pediatric use of SonoVue in echocardiography, nor is Bracco aware of registries that may be used to obtain information on the use of SonoVue to improve EBD in pediatric subjects.

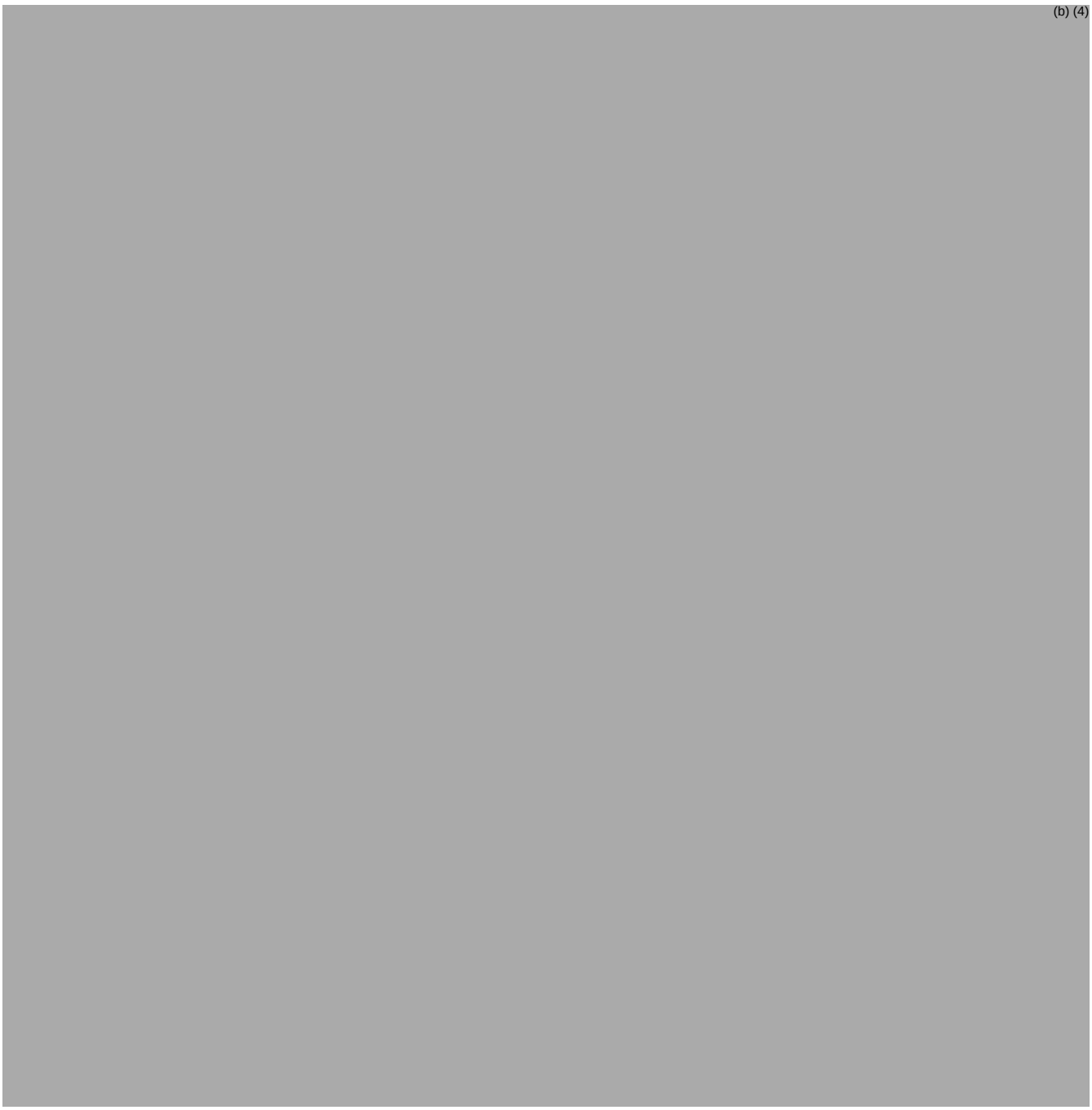
However, Bracco acknowledges that published literature suggests the occurrence of technically suboptimal echocardiographic windows resulting in suboptimal echocardiograms may occur in children and adolescents during rest echocardiography, even if significantly less frequent than in adults.

Bracco conducted a survey from 10 cardiologists with experience in pediatric cardiology from 10 different cardiovascular centers in the United States having well-established departments of pediatric cardiology in order to understand how often contrast is used in pediatric echocardiography and in which age groups. The results showed that 8 of the 10 centers surveyed do not use ultrasound contrast in their pediatric cardiac centers. One center uses it in rare instances for non-cardiac use in muscular dystrophy in patients aged 14-20 years and one center uses it occasionally for myocardial perfusion imaging, but not for EBD, during stress examination in patients aged 15-20 years with Kawasaki, a very rare disease.

In view of the results of this survey and of the absence of evidence of use of ultrasound contrast in pediatric patients younger than 9 years of age undergoing rest echocardiography, Bracco proposes to conduct a study that is designed to assess the efficacy of SonoVue-enhanced echocardiography vs. unenhanced echocardiographic imaging in a pediatric population of age 9 to 17 years with poor transthoracic image quality and suboptimal EBD and to exclude younger patients for whom the risk-benefit of contrast enhancement is totally unknown.

The waiver request and justification is provided on the following pages.

(b) (4)



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(b) (4)

9.4 Justification for Waiver of Pediatric Assessment Requirements

Bracco is only requesting a Partial Waiver of pediatric studies only in the age group of below 9 years of age based on the absence of clinical data in that specific subset of the pediatric population undergoing rest echocardiography.

Bracco conducted a survey from 10 cardiologists with experience in pediatric cardiology from 10 different cardiovascular centers in the United States having well-established departments of pediatric cardiology in order to understand how often contrast is used in pediatric echocardiography and in which age groups. The results showed that 8 of the 10 centers surveyed do not use ultrasound contrast in their pediatric cardiac centers. One center uses it in rare instances for non-cardiac use in muscular dystrophy in patients aged 14-20 years and one center uses it occasionally for myocardial perfusion imaging, but not for EBD, during stress examination in patients aged 15-20 years with Kawasaki, a very rare disease.

In view of the results of this survey and of the absence of evidence of use of ultrasound contrast in pediatric patients below 9 years of age undergoing rest echocardiography, Bracco proposes to conduct a study that is designed to assess the efficacy of SonoVue-enhanced echocardiography vs. unenhanced echocardiographic imaging in a pediatric population of age 9 to 17 years with poor transthoracic image quality and suboptimal EBD and to exclude younger patients for whom the risk-benefit of contrast enhancement is totally unknown.

The type, frequency and severity of adverse events observed following intravenous administration of SonoVue in pediatric patients are similar to those observed in adults; therefore, the risk-benefit ratio of the use of SonoVue in pediatric patients above 9 years of age with suboptimal echocardiograms is expected to be the same as in adults with suboptimal EBD. Instead, in children below 9 years of age, no benefit is expected. Therefore, per section 505B (a) (4) (A) (i) of the PREA, Bracco respectfully requests that the Agency grant a waiver of the pediatric assessments requirement for SonoVue in the cardiac left ventricular opacification/endocardial border delineation indication in the pediatric population under 9 years of age.

9.5. Summary Table of Planned Clinical Studies

Nonclinical studies are not planned. **Table** 34 summarizes the planned clinical study in the pediatric patient population inclusive of pharmacokinetics assessment of SF_6.

9.6 Pediatric Formulation Development

PREA requires pediatric assessments to be gathered using appropriate formulations for each age group for which the assessment is required (section 505B(a)(2)(A) of the Act). In the case of SF_6 microspheres, the formulation is a lyophilized powder, which is reconstituted with a solvent (0.9% NaCl solution) to produce an aqueous suspension of microspheres. This suspension is then administered intravenously by a healthcare professional (physician, nurse or sonography technician) during the course of an ultrasound examination. Because of the nature of the product, the route and the method of administration, the sponsor does not believe that a specific formulation is required for the performance of studies in the pediatric population.

9.7 Pharmacokinetic Studies

SonoVue has a well-established pharmacokinetic profile that has been studied and characterized in clinical trials in adults with healthy and impaired lungs.

The gas phase in the SonoVue vial is an innocuous gas hexafluoride (SF_6). The total amount of SF_6 administered in a clinical dose is extremely small (2 mL dose contains 16 µL of SF_6 microspheres). Most or all of the SF_6 from a SonoVue dose rapidly dissolves in the blood and subsequently eliminates by the lungs. The cumulative recovery of SF_6 in expired air averaged 86% to 94% of the administered dose in healthy subjects. Furthermore, the recovery of SF_6 in expired air in subjects with impaired lungs averaged 102%. This finding indicates that the patients eliminate all of the SF_6 from SonoVue via their lungs rather than an alternate elimination route, despite the impairment of lung function. In addition, a published study by Morel et al. had shown that SonoVue rapidly removed from the blood by the pulmonary route with 40% to 50% of the injected dose eliminated within the first minute after administration and 80% to 90% eliminated by 11 minutes after administration. Most alveolar maturation occurs in the first 2 years of life, so that no differences in the elimination of the gas between adults and pediatric patients 9-17 years-old should be expected.

The pharmacokinetics of SonoVue have been previously tested in adults through the analysis of SF_6 from expired air and blood samples taken sequentially over approximately 60-120 minutes post dose. The method for collection of exhaled air is technically challenging and also dependent on a high degree of patient compliance. The technique involves collection of expired air into plastic bags via a respiratory mask and the use of a pulmonary monitoring system (e.g., Spirobank). Collection of expired air continues up to 120 min post dose. Apparently, such a level of compliance cannot be expected from children unless they are appropriately sedated during the whole procedure.

In addition, conducting a comprehensive pharmacokinetic study in healthy children administered SonoVue would be not feasible since the children enrolled in such a study would not gain any benefit from exposure to SonoVue while in order to detect the small quantities of SF_6 in expired air, doses 10 times higher than the proposed efficacious SonoVue dose may be needed. We would anticipate overwhelming ethic obstacles in obtaining approvals from Institutional Review Boards (IRB) and Ethics Committees (EC), considering unfavorable risk-benefit ratio for this type of study.

Besides, to have patients undergo such a study, they should be referred for contrast enhanced echocardiography due to suboptimal rest images acquired over conventional echocardiography and have the need for visualization of EBD for diagnostic purposes. In order to obtain SF_6 concentrations in expired air samples, besides the challenges described above, the technique of expired air collection will interfere with image acquisition in echocardiography because of a big plastic bag utilized in the expired air collection and the position of the patient for the ultrasound examination.

9.8 Planned Clinical Effectiveness and Safety Studies

(b) (4)

9.10 Plan to Request Deferral of Pediatric Studies

Bracco does not request a deferral of pediatric studies.

9.11 Agreements for Pediatric Studies with Other Regulatory Authorities

Bracco does not have any agreements in place for pediatric studies with other Regulatory Authorities.

9.12 Medical Reviewer's Assessment of Pediatric Development Plan

With reference to the FDA's Complete Response letter to their pending application for SonoVue received October 19, 2012 and in compliance with the Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act*, published in September 2005, Bracco Diagnostics Inc. has submitted the following Pediatric Study Plan (PSP). Further reference is made to pediatric studies required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), as all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable

The primary objective of your study is to assess the efficacy of Vueson--enhanced echocardiography in improving left ventricular (LV) EBD in pediatric patients with suboptimal LV EBD at unenhanced echocardiography. The adult proposed Package Insert indication wording is as follows:

"SonoVue is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial border."

DMIP recommends requesting that the sponsor provide:

1. Success criteria (specific EBD score difference between the CEUS and UEUS required for determination of trial success) and timing of endpoint assessments.

2. A statistical approach (e.g., statement of null and alternative hypotheses, sample size/power justification).

3. [redacted] (b) (4) DMIP recommends that the sponsor provide adequately powered data to support both the EBD and opacification endpoints similar to the indication for adults.

4. Please provide justification and statistical support for the number of patients age 9 to 17 that will be evaluated.

5. Please remove [redacted] (b) (4) from the exclusion criteria or provide justification for not removing them.

6. Consider stopping administration to additional pediatric subjects and reassess safety if serious or severe adverse reactions possibly related to the drug are identified. Compliance with label BLACK BOX WARNING to "Always have resuscitation equipment and trained personnel readily available" in case of a serious cardiopulmonary reaction.

7. Add a secondary endpoint to substantiate the percentage of patients converting from sub-optimal to adequate imaging post contrast administration.

8. The label should state that the maximum dose in children [redacted] (b) (4) not exceed the recommended dose for adults (2.0 mL).

9. A list of planned laboratory Evaluations proposed pre- and post- administration of SF-6.

In compliance with the FDA request, the sponsor has provided:

1. A satisfactory overview of the drug product, SF6, as utilized for contrast-enhanced ultrasonography.

2. A satisfactory overview of the rarity of diseases for which this drug product would be beneficial when utilized within the pediatric population.

3. A proposed pharmacokinetic study among 6 patients aged 9-12 (3 males and 3 females) and among 6 patients aged 12-17 years (3 males and 3 females).

Results from pharmacokinetic studies in adults and adequate justifications for not performing similar studies in children under the age of 9.

4. Adequate support for requesting a partial waiver to exclude assessment of children less than 9 years of age based on the limited applicability to that specific age group and the drug product offering no meaningful therapeutic benefit over existing non-contrast ultrasound.

5. Adequate plans for a clinical effectiveness and safety study among 9 to 17 year olds with Table of planned clinical study. Their drug product will be studied within 92 patients (b) (4)

6. A reasonable assessment for an appropriate formulation for administration to the 9 to 17 year pediatric age group. In the case of SF_6 microspheres, the formulation is a lyophilized powder, which is reconstituted with a solvent (0.9% NaCl solution) to produce an aqueous suspension of microspheres. In adults, the dose for left ventricle opacification is a fixed dose of 2 mL. (b) (4)

7. Support that a specific pediatric formulation is not required because of the nature of the product, the route and the method of administration. This suspension is administered intravenously by a healthcare professional (physician, nurse or sonography technician) during the course of an ultrasound examination.

8. A proposed tentative action plan that is acceptable.

9. Whereas, considerable clinical experience and data are available regarding SF6, no non-clinical studies are planned.

10. Extrapolation of data from the adult to pediatric population is not applicable because the sponsor intends to perform a pediatric clinical study to establish PK, efficacy and safety within patients aged 9 through 17 years. The efficacy phase of the study will compare patients' post-contrast images to their pre-contrast images.

(b) (4)

10. Product Naming

The Sponsor has submitted a variety of potential names for their SF6 (sulfur hexafluoride) microbubble drug. Within this document SF6 is referred to by an assortment of potential names such as SonoVue, (b) (4) and most recently Lumason. In all cases where referenced in this document, these names should be considered to be interchangeable. As of this date, final determination of an approved name has not been completed.

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/s/

SCHELDON KRESS
11/05/2013

BRENDA Q YE
11/05/2013
I agree with Dr. Kress' assessment.

Medical Officer's Labeling Review
Response to OPDP Consult [Oct 15, 2013]

NDA:	**203684**
Product:	Lumason
Applicant	Bracco Diagnostics
Reviewer:	Scheldon Kress, MD, DMIP, OND, CDER
Through:	Louis Marzella, MD, Acting Director, DMIHP, OODP, CDER
Date:	November 1, 2013

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on July 2, 2013, for (b) (4) (Sulfur Hexafluoride Microbubbles). They provided comments on the PI based on the proposed labeling emailed on October 2, 2013. OPDP's comments included a marked-up copy of the proposed PI. OPDP made the following recommendations and DMIP actions follow:

OPDP Recommendations	DMIP Actions
Revising the Highlights to include: Cardiopulmonary resuscitation personnel and equipment should be readily available prior to administration of the drug and to monitor all patients for acute reactions. It is included in the Highlights section of the Definity PI.	**Added to Highlights:** Always have resuscitation equipment and trained personnel readily available.
Consider revising the Highlights to include: drug should not be administered by intra-arterial injection. Definity PI includes this information in this section.	**Added to Highlights:** Do not administer by intra-arterial injection,
Competitor labels (Optison, Definity) describe the anaphylactoid reactions as "uncommon but serious." We recommend revising this section and the Highlights to include the term "serious" to describe the reactions to avoid minimizing the risks of the drug and for consistency with competitor labels.	Serious is covered in 5.1 immediately above and 5.2 covers anaphylactic shock being uncommonly observed. Anaphylactic shock by itself always implies a serious condition.
Consider deleting and reinstating the original language: "In patients"	Wording not necessary.
We note that the Definity PI states, "greater sensitivity of some older individuals cannot be ruled out." Does this also apply to (b) (4)? If appropriate, please consider including this language.	We have no evidence for greater sensitivity among older individuals.

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/s/

SCHELDON KRESS
11/04/2013

Office Director Action Memo

Date	October 15, 2012
From	Charles J. Ganley, MD
Subject	Office Director Action Memo
NDA/BLA #	NDA: 203-684
Applicant Name	Bracco Diagnostics, Inc.
Date of Submission	December 21, 2011
PDUFA Goal Date	October 21, 2012
Proprietary Name / Established (USAN) Name	"Sonovue" was proposed and rejected by FDA Sulfur hexafluoride lipid microspheres
Dosage Forms / Strength	The drug is supplied as a kit that is composed of: a glass vial containing 25 mg powdered sulfur hexafluoride lipid microspheres; a prefilled syringe containing 5 mL saline (diluent); and a transfer device for attaching the syringe to the vial.
Proposed Indication(s)	"SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation."
Action/Recommended Action	Complete Response based on deficiencies identified during the inspection of the manufacturing facility.

Sulfur hexafluoride lipid microspheres are an ultrasound contrast agent whose purpose is to enhance the delineation of the heart borders during echocardiogram examination in patients with suboptimal echocardiograms. The application was originally submitted in 2001 but was later withdrawn because of reports of serious adverse events post-marketing in Europe. The product continues to be marketed in Europe. The history of these types of products is described in the clinical memos. The DRISK memo provides a comprehensive summary of the history related to this product. A box warning was added to this class of products in 2007. An FDA advisory committee opined on the data related to serious adverse events in 2008 for this class of drugs. The events are uncommon and a revised box warning remains on the approved products.[1]

The product kit contains a vial containing 25 mg of sulfur hexafluoride (SF6) lipid lyophilized powder microspheres, a pre-filled syringe containing 5 ml of 0.9% sodium chloride (diluent) and a Mini-spike (b) (4) (b) (4) transfer system (to transfer the diluent into the vial and then to withdraw the reconstituted product into the syringe).

There are no outstanding CMC issues or microbiology issues that require resolution. There are some facility inspections issues related to the manufacturing facility that are discussed below and form the basis for withholding approval of the application at this time. The product should have a milky white appearance after reconstitution and should be used with 3 hours. The shelf life of the lyophilized powder is 24 months. The expiration date for the saline syringe is 36 months.

There are no pending nonclinical pharmacology/toxicology issues.

There are no outstanding clinical pharmacology issues. The SF6 concentration peaked in 1 to 2 minutes. The terminal half-life is approximately 10 minutes with the majority being eliminated in expired air. In subjects with pulmonary impairment, the terminal half-life was similar to healthy subjects. The sponsor conducted dose response studies to evaluate improvement in border delineation as a function of dose and these were further evaluated in the clinical efficacy studies.

[1] Definity and Optison are approved products

The brand name Sonovue was not found acceptable by the Division of Medication Error Prevention and Analysis.

The clinical efficacy data in the application is the same data in the 2001 submission. It was reviewed based on current typical imaging standards. The clinical reviewer, clinical team leader, statistical reviewer and division director believe that the drug improves the delineation of the cardiac borders. The sponsor submitted three studies to support the efficacy. Multiple doses were evaluated in each study. 2D echocardiography was obtained prior to injection and continued to at least 15 minutes after dosing. Two readers blinded to dose and clinical history evaluated the echocardiograms. In all studies, the ability to delineate the cardiac borders was improved with sulfur hexafluoride lipid microspheres. A 2 ml dose was determined to be adequate. The mean duration of useful contrast effect was 1.7 – 3.1 minutes. In the review of safety data, the primary safety concern involved anaphylactoid type reactions and serious cardiovascular events occurring almost immediately after injection. These are rare occurrences and are similar to reports observed with other products in this class. A box warning describes the serious cardiovascular reactions and the anaphylactoid reactions are described in the label. There are no additional safety studies recommended at this time.

There are two outstanding issues that require resolution prior to approval. First, the manufacturing facility failed its inspection. A 483 was issued to the sterile drug manufacturer, Bracco Suisse SA, which contains multiple deficiencies that require resolution before the application can be considered for approval. There are also issues related to the quality of the product which are addressed in the Establishment Inspection Report and will require resolution prior to approval. Second, the transfer device included in the kit is not cleared in a 510(k) by CDRH. The sponsor will have to resolve this issue prior to approval.

Conclusion
Because of deficiencies in the inspection of the sterile drug manufacturer, the application cannot be approved at this time. The transfer device is not cleared in a 510(k). The sponsor will have to resolve these issues before approval. A complete response letter will be issued.

Recommendation
Complete response letter.

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/s/

CHARLES J GANLEY
10/16/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203684
Priority or Standard	Standard
Submit Date(s)	December 21, 2011
Received Date(s)	December 21, 2011
PDUFA Goal Date	October 21, 2012
Division / Office	CDER/OND/DMIP
Reviewer Name(s)	Scheldon Kress, M.D.
Review Completion Date	August 24, 2012
Established Name	**Sulfur hexafluoride (SF6) microspheres**
(Proposed) Trade Name	SonoVue
Therapeutic Class	Suspension for Injection
Applicant	Bracco
Formulation(s)	**Sulfur hexafluoride (SF6) microspheres**
Dosing Regimen	2.0 mL. during a single examination
Indication(s)	**SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation**
Intended Population(s)	**Patients with suboptimal echocardiograms**

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

Based on the clinical review of study design, conduct and the analysis of study results, substantial evidence of effectiveness of SonoVue has been demonstrated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation. SonoVue suspension in saline, consists of microspheres containing the innocuous gas sulfur hexafluoride (SF6) covered by a monolayer lipid shell. It is administered as an intravenous bolus injection during echocardiography.

The microspheres (also referred to as microbubbles) do not diffuse extra-vascularly and remain within the blood vessels. The microbubbles are smaller than red blood cells, are durable, traverse the pulmonary circulation and can be visualized within the ventricles by utilizing ultrasound. With ultrasound, these microbubbles, serve as echogenic contrast agents by causing scattering and reflections of resonating ultrasound waves thereby making them detectable while within the ventricles.

Clinical Trial Conclusions - 019A, 019B, & 013

There was a significant increase of EBD scores when compared to baseline unenhanced echocardiography. An increase of total LV EBD score from baseline of ≥4 was observed in 42% to 98% of patients for the SonoVue dose groups.

Higher percentage of patients converted from suboptimal to adequate image quality. In studies BR1-019A and BR1-019B, the percentage of patients with LVO scores of +2 or +3 (moderate or complete opacification) ranged from 73% to 93% across all off-site readers and across all SonoVue doses.

Reduction in the proportion of patients with inadequate EBD in ≥1 segment, ≥2 segments, ≥2 adjacent segments, and in at least 1 or 2 critical segments (distal part of main branch coronary artery) could be observed with SonoVue.

Based on study results, the useful contrast effect and endocardial delineation scores increased as doses of SonoVue increased from the 0.05 mL through the 2.0 mL dose. However, the 4.0 mL highest dose evaluated did not demonstrate any advantage over the 2.0 mL dose. Therefore, we agree that the data support the selection of the 2 mL dose as the proposed marketing dose.

Analysis of carry-over effect demonstrated the absence of carry-over effects and supported a strong dose-response relationship.

Similar to other intravenously administered microspheres utilized for contrast enhancement of ultrasound cardiac imaging, SonoVue has the potential to be associated with the immediate onset of serious life-threatening events. SAEs that can occur involve the immune, cardiac, vascular, respiratory, and nervous systems. Whereas the safety profile of SonoVue is comparable to that of the other ultrasound contrast agents already marketed in the United States, Definity and Optison, all members of this class of contrast imaging agents, ultrasound microspheres, carry a similar Black Box Warning within their label.

Physicians administering these agents may need guidance in management of these SAEs. As demonstrated in the case reports of deaths provided, when confronted with such emergencies in patients with known coronary artery disease, clinicians have had difficulty distinguishing cardiac from anaphylactic causation, thus impeding timely initiation of proper therapeutic measures. Availability of this information may be beneficial in providing guidance to assist clinicians when suddenly faced with such medical emergencies.

Risk Benefit Assessment

Risk minimization measures include the proposed package insert and routine pharmacovigilance surveillance:

From the proposed package insert:

- Section 4 (contraindications) indicates that SonoVue is contraindicated in patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue
- Section 5 (warnings and precautions) states that rare cases of serious cardiopulmonary reactions, including fatalities, have occurred following the injection of sulfur hexafluoride containing microbubbles. The increased risk for these reactions in patients with unstable cardiopulmonary conditions and the type of reported reactions are included in this section, together with the recommendation to always have cardiopulmonary resuscitation personnel and equipment readily available prior to administration of SonoVue
- The proposed boxed warning refers to the risk of serious cardiopulmonary

reactions after the administration of SonoVue reporting the following wording: rare cases of serious cardiopulmonary reactions, including fatalities, have occurred following the injection of sulfur hexafluoride containing microbubbles. Most serious reactions occur within 30 minutes of administration. Assess all patients for the presence of any condition that precludes SonoVue administration. Always have resuscitation equipment and trained personnel readily available.

Routine pharmacovigilance activities include:

- Systematic collection of adverse events from multiple sources (including cases that originate from literature)
- Expeditious and periodic medical assessments of single and aggregate reports
- Identification of potential safety signals
- Evaluation of the risk-benefit balance of the product through its life cycle.

The three (3) deaths probably attributed to SonoView demonstrated a similar pattern, an anaphylactic or anaphylactoid reaction immediately (seconds to minutes) following the intravascular administration of Sonovue. In general, the observed pattern of these cases considered as probably related to the administration of Sonovue are very similar to those reported with other intravenous medical imaging microspheres (or microbubbles). Symptoms start a few seconds or minutes after intravenous contrast administration. Sometimes the events start with mild symptoms and then a drop in blood pressure, dyspnea and/or loss of consciousness are observed; sometimes they are already severe from the beginning. Of note, no skin or mucosal symptoms were ever observed in these cases. In all cases, underlying conditions of the patients may have contributed to the fatal outcome. These three patients suffered from significant coronary artery disease. In two cases, Sonovue was administered to patients with ongoing acute myocardial infarctions. Of note, in both cases no specific treatment for the underlying myocardial infarction was given, but only treatment for anaphylaxis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Agency had been in discussions with the sponsor regarding the design of a large postmarketing safety study among patients with significant cardiovascular disease. However, these discussions did not yield an agreed upon study design.

1.4 Recommendations for Postmarket Requirements and Commitments

Whereas there exists an extensive European experience with exposure of approximately (b) (4) patients and a relatively small rate of reported serious cardiopulmonary reactions associated with the use of SonoVue, no Risk Management Plan is being proposed. The risks associated with SonoVue administration will be managed through labeling and inclusion of a Boxed Warning for the serious risk of cardiopulmonary reactions. No postmarketing requirements are being planned at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Sulfur hexafluoride microbubbles are formulated as 25 mg sterile, non-pyrogenic lyophilzed powder in a (b) (4) sealed vial. The gas phase in the vial is SF6, an innocuous gas + monolayer lipid shell ((b) (4) DSPC, (b) (4) DPPG.Na and (b) (4) palmitic acid) (**Figure 1** and **Figure 2**). The suspension for injection is reconstituted with 5 ml of saline. The recommended dose is 2 mL administered as an intravenous bolus injection during echocardiography.

Figure 1 : Composition of gas

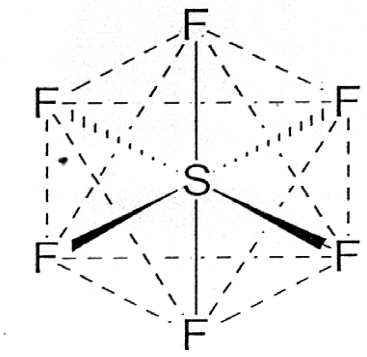
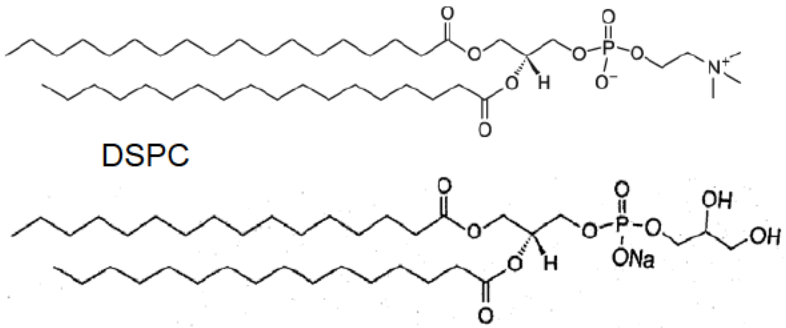


Figure 2 : Lipid Composition of Shell



DSPC

DPPG.Na

The microbubble concentration administered is 8 µL/mL. The mean diameter of a microbubble is 1.5-2.5 µm and 90% of the microbubbles are (b) (4) and 99% are <11 µm. (**Figure 3**)

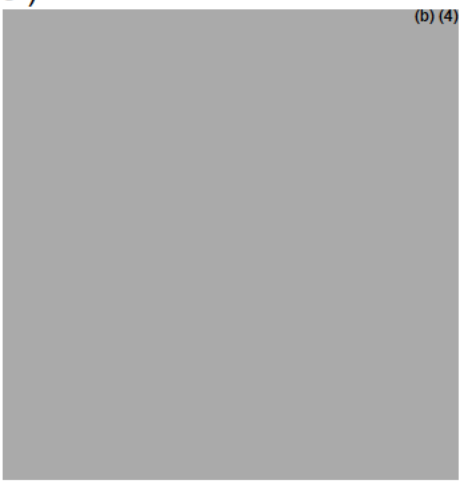


Figure 3 : SonoVue Microsphere

Sulfur hexafluoride microbubbles are administered intravenously. The microbubbles do not diffuse extra-vascularly and remain within the blood vessels. The microbubbles are smaller than red blood cells, are durable, traverse the pulmonary circulation and can be visualized within the left ventricle via ultrasound.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 : Comparison of Microsphere Products Indicated for Use in Patients with Suboptimal Echocardiograms to Opacify the Left Ventricle and Improve the Delineation of the Left Ventricular Endocardial Borders

Product	Gas Filling	Outer Shell	Mean Diameter	IV Bolus Dosing
SonoVue*	Sulfur hexafluoride	Lipid	1.5-2.5 µm	2.0 mL
Optison	Octafluoropropane:	Human albumen	3.0-4.5 µm	0.5 mL
Definity	Octafluoropropane	Lipid	(b) (4) µm	10 µL/kg

* Pending approval of this application

2.3 Availability of Proposed Active Ingredient in the United States

Sulfur hexafluoride (SF6) microspheres is not currently available for general use within the United States except under IND investigations. SonoVue is currently approved in 36 countries and marketed in 25 countries, for:

- Opacification of cardiac chambers
- Enhance left ventricular endocardial border deliniation
- Enhance echogenicity of blood for:
  - Doppler of Macrovasculature
    - Cerebral arteries
    - Extra-cranial carotid arteries
  - Doppler of Microvasculature
    - Vascularity of liver
    - Vascularity of breast

2.4 Important Safety Issues with Consideration to Related Drugs

Similar to other intravenously administered microspheres (microbubbles) utilized for contrast enhancement of ultrasound imaging, Sonovue has the potential to be associated with the immediate onset of serious life-threatening events. SAEs that can occur involve the immune, cardiac, vascular, respiratory, and nervous systems. Those SAEs and deaths that have been observed, usually occur immediately or within minutes following intravenous administration.
When utilized to evaluate echocardiographic abnormalities during drug induced pharmacologic stress, one can expect a higher incidence of adverse events as the drugs utilized to induce these physiologic changes are associated with a significant adverse event profile.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Clinical trials were initiated under IND 46958 in 1994. NDA 21315 was submitted in 2001 and underwent multiple revisions. [redacted] (b) (4) the NDA was withdrawn.

In 2008, Bracco was invited to present their SonoVue ultrasound safety data to a CRDAC that would review safety issues related to ultrasound contrast agents, all microbubbles.

In 2009, Bracco met with DMIP to discuss a new submission. The pre-NDA meeting resulted with the following agreements with the FDA:

- FDA agreement
  - Primary database could rely on the 3 prior confirmatory studies
- FDA recommendations to complete prior to NDA submission:
  - Pulmonary hemodynamic study
  - Retrospective observational study among critically ill patients
- FDA recommended completion as Post-marketing Requirement
  - 1,000 subject prospective “safety study”

At the 2011 CRDAC, safety of all USC Agents were reviewed, concerns were raised regarding safety of USCA and the members agreed:

- Validity of retrospective studies was questionable
- [redacted] (b) (4) and propensity score analyses had limitations
- Absence of significant pulmonary hemodynamic effects by USCA

Based on CRDAC assessment, the members arrived at the following conclusions:

- Understanding of safety risk of USCA was evolving
- Risks exist, but events appear to occur randomly
- Re-assessments led to reduced scope of Black Box warnings

Following the CRDAC meeting, Bracco requested guidance from the FDA for going forward with their upcoming submission. Meeting with the FDA in 2011, 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]

2.6 Other Relevant Background Information

Clinical Development Program

Clinical Pharmacology Exploratory Studies

Clinical pharmacology exploratory studies to assess the preliminary efficacy of SonoVue for EBD and LVO; the results of these studies provided the basis for the Phase II/III program to evaluate the use of SonoVue for EBD.

BR1-001	Safety and tolerability of single ascending dose during 2D echocardiograpy in 36 healthy volunteers
BR1-002	Safety and tolerability during Repeat ascending cumulative dose 2D Echocardiography in 30 healthy volunteers
BR1-005	Open-label, crossover with 4 doses in 36 patients with cardiac disease referred for echocardiography and having suboptimal endocardial border detection with unenhanced ultrasound
BR1-007	Safety and tolerability during repeat fixed doses 2D echocardiograpy with multiple transducer frequencies in 10 healthy volunteers
BR1-010	Evaluate pharmacokinetic parameters of SF6 in blood and exhaled air

Prospective Phase II/III supportive Studies

Two prospective Phase II/III studies in 437 patients with known or suspected cardiac disease to determine the efficacy of SonoVue over a range of doses (0.5, 1, 2, and 4 mL) in patients with known or suspected cardiac disease referred for 2D transthoracic echocardiography at rest (BR1-011) or during rest and pharmacologically-induced stress (BR1-012). BR1-011tested 4 doses at rest (218 patients) and BR1-012 tested 2 doses at rest and stress (219 patients).

Study BR1-011 assessed endocardial border delineation at rest and to determine EF compared with that from a reference standard. Study BR1-012 assessed patients randomized to receive one of the four SonoVue doses during echocardiography at rest and again during pharmacological stress (arbutamine or dobutamine were the stress agents used). The primary efficacy endpoints were change from baseline in endocardial border delineation based on total view score (total view score included segment scores obtained from apical and parasternal views; 0-44) and total apical view score (0-24). Efficacy assessments for each study were performed on-site unblinded) by the investigator and off-site by four blinded, independent echocardiographers (two pairs of offsite readers; each pair independently assessed half of the total number of patient images for the study).

Confirmatory Phase 3 Studies

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). These studies were performed during 1996-7. These studies included 317 patients of which 191 received SonoVue.

A total of 866 subjects participated in these studies; 718 received SonoVue and 148 received control only. Among the 718 who received SonoVue, 53 received both SonoVue and control agent (crossover study BR1-013).

Additional Ongoing Studies

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All studies in the SonoVue EBD Clinical Program are in accordance with the ethical principles as outlined in the Declaration of Helsinki and were conducted in compliance with the regulations and guidelines released by the U.S. FDA, the European Union (EU), and the International Conference on Harmonization, including:

- Choice of control groups in clinical trials (ICH Topic E10, Note for Guidance on Choice of Control Groups in Clinical Trials, CPMP/ICH/364/96)

- Structure and content of clinical study reports (ICH Topic E3, Note for Guidance on Structure and Content of Clinical Study Reports, CPMP/ICH/137/95).

Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol was obtained prior to initiation of each study. A written informed consent was obtained from each subject before any study procedures were performed. In addition, although conducted in 1996 and 1997, the conduct and design of the 3 confirmatory studies are in accordance with the Guideline on Clinical Evaluation of Diagnostic Agents CPMP/EWP/1119/98/Rev. 1, July 2009:

Bracco Diagnostics Inc. certified that it did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this submission.

3.2 Compliance with Good Clinical Practices

All studies in the SonoVue EBD Clinical Program are in accordance with the Good Clinical Practice (International Conference on Harmonization [ICH] Topic E6, Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95; EU Council Directive 75/318/EEC)

3.3 Financial Disclosures

The sponsor provided a list and certified that none of the listed clinical investigators for Studies BR1-019A, BR1-019B and BR1-013 entered into any financial arrangement whereby they could benefit from the outcome of the study or had an equity or proprietary interest in this product. Furthermore, none of the listed investigators was a recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Sulfur hexafluoride microbubbles are formulated as 25 mg sterile, non-pyrogenic lyophilized powder in a (b) (4)-sealed vial. The vial contains SF6, an innocuous gas, the lipid shell components (DSPC and DPPG.Na)1 and palmitic acid as a stabilizer. The suspension for injection is reconstituted with 5 ml of saline. After shaking, the lipids form a monolayer surrounding the core gas, the SonoVue microbubble.

The microbubble concentration administered is 8 µL/mL. The mean diameter of a microbubble is 1.5-2.5 µm and 90% of the microbubbles are (b) (4) and 99% are <11 µm.

4.2 Clinical Microbiology

This is a non-therapeutic drug. CMC evaluation was acceptable.

1 DSPC =distearoylphosphatidylcholine and DPPG.Na = Dipalmitoylphosphatidylglycerol sodium

4.3 Preclinical Pharmacology/Toxicology

The nonclinical testing strategy followed the recommendations of the FDA Guidance Document "Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application (Posted 3/2/1998)" and of the ICH guideline "M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals".

In addition to the standard nonclinical pharmacology, pharmacokinetic and toxicology studies required by the FDA and international regulatory agencies, several nonclinical studies were performed after marketing SonoVue® worldwide (except in the USA) to contribute to an understanding of the mechanism of the rare cases of severe adverse events (SAR) observed with the product and similar ultrasound contrast agents.

The majority of the nonclinical studies, with the exception of the reproduction toxicology studies, were performed using the first formulation of SonoVue® studied clinically, which did not contain palmitic acid. Palmitic acid is an endogenous blood component that is measured along with other fatty acids when performing standard blood chemistry tests. The endogenous amount of palmitic acid in blood is in the order of 29 mg/L. In comparison, the blood concentration of palmitic acid following a 2 mL clinical dose of SonoVue® for imaging cardiac cavities is 0.0032 mg/L. Palmitic acid is also a natural component of food that can be present in large quantities in the blood after a meal. Depending upon the amount of palmitic acid present in a meal, palmitic acid may represent up to 25% of all circulating fatty acids. Considering that 1) the amount of palmitic acid added to the final formulation is small, and 2) palmitic acid is a dietary fatty acid which can be present in large quantity in blood after a meal, additional toxicology studies on the final marketed formulation were not considered necessary. Palmitic acid was added to the formulation to stabilize the microbubbles.

4.4 Clinical Pharmacology

Mechanism of Action

Sulfur hexafluoride microbubbles are administered intravenously. The microbubbles do not diffuse extra-vascularly and remain within the blood vessels. The microbubbles are smaller than red blood cells, are durable, traverse the pulmonary circulation and enter the left ventricle. Echogenic contrast agents cause scattering and reflections of resonating ultrasound waves thereby making them detectable while within the ventricles.

The acoustic properties of SonoVue and the resistance of the reconstituted preparation to pressure were studied *in vitro*. *In vivo* imaging studies were conducted in dogs, minipigs, sheep, and rabbits. Studies elucidating the basic characteristics of SonoVue and early imaging results in animals are also reported in the literature. In addition, a

series of animal and *in vitro* experiments were conducted to study the possible mechanism of actions for the serious adverse reactions (SAR) observed after administration of SonoVue® in a low percentage of patients (overall current SAR-reporting rate of 0.012%) in countries where it is marketed. The safety pharmacology and potential pharmacodynamic drug interactions of SonoVue were also studied in a series of *in vitro* and *in vivo* pharmacology studies.

4.4.2 Pharmacodynamics

Pharmacokinetics

Results of the clinical pharmacology/exploratory studies demonstrated that SonoVue was well tolerated, was capable of traversing the pulmonary circulation, providing opacification of both the right and the left cardiac chambers and improving the endocardial border detection in the left ventricular cavity with respect to placebo. The optimum imaging frequencies functioned well at 3.5 MHz. The pharmacokinetics of SF_6 following intravenous bolus administration of SonoVue has been characterized in two of the studies at the doses of 0.03 mL/kg and 0.3 mL/kg.

Following intravenous mixing of the suspension, the microbubbles attain a final concentration of 8 µL/mL. Recommended dose for adults and the elderly, at rest or with stress for 2D imaging of cardiac chambers is 2.0 mL. A second injection can be administered during a single examination.

Following intravenous administration, the microbubbles attain maximal concentration within the heart for 1 to 2 minutes, then the gas is rapidly eliminated via the expired air.

5 Sources of Clinical Data

Tables of Studies/Clinical Trials

The study design and efficacy assessments for the Phase III program are summarized in **Table 2** and described in detail in the following text.

Table 2 : Phase II/III Clinical Studies That Contribute to the Evaluation of Efficacy of SonoVue

Protocol Number	SonoVue Dose (mL)[a]	Patient Population	No. Treated	Study Design	Control Agent	Dose (mL/kg)	Efficacy Endpoints
BR1-019A	0.5 1.0 2.0 4.0	Patients with suspected cardiac disease and suboptimal border delineation on unenhanced 2D transthoracic echocardiography at rest	143 (76/67)[b]	Single-blind, parallel-comparative, crossover-dose ranging study in USA	Albunex 0.9% Saline	0.08 0.22 0.08 0.22	- EBD score - LVO score - contrast duration - contrast shadowing - confidence in diagnosis
BR1-019B	0.5 1.0 2.0 4.0	Patients with suspected cardiac disease and suboptimal border delineation on unenhanced 2D transthoracic echocardiography at rest	121 (62/59)[b]	Single-blind, parallel comparative, crossover-dose ranging study in USA	Albunex 0.9% Saline	0.08 0.22 0.08 0.22	- EBD score - LVO score - contrast duration - contrast shadowing - confidence in diagnosis
BR1-013	1.0 2.0	Patients with suspected cardiac disease and suboptimal border delineation on unenhanced 2D transthoracic echocardiography at rest	53 All patients received both SonoVue and Albunex	Single-blind, crossover study in USA	Albunex	0.22	- EBD score - LVO score - contrast duration - ejection fraction - wall motion

EBD, endocardial border delineation; LVO, left ventricle opacification; 2D, 2-dimensional
[a] Each mL of SonoVue dispersion contains 8 µL SF_6 in the microbubbles.
[b] Number of patients who received SonoVue / number of patients who received control.

5.2 Review Strategy

Discussion of Individual Studies/Clinical Trials

The clinical pharmacology/clinical studies were designed to demonstrate that SonoVue was well tolerated, capable of traversing the pulmonary circulation, providing opacification of both the right and the left cardiac chambers and improving the endocardial border detection in the left ventricular cavity with respect to placebo.

A total of 866 subjects participated in these studies; 718 received SonoVue and 148 received control only. Among the 718 who received SonoVue, 53 received both SonoVue and control agent (crossover study BR1-013).

Patients were examined in either the supine or lateral decubitus position. Every effort was made to keep the optimal transducer position unchanged during the entire echocardiographic study for each patient. A recording of 2D trans-thoracic echocardiography was made from 30 seconds prior to injection of each dose of study agent and continued for at least 15 minutes after injection or until the end of the contrast effect (return to baseline), whichever was longer. For pre- and post-injection images, the apical four-chamber view was recorded first followed by the apical two-chamber view. The exploration of each view was obtained in 15 to 30 second intervals. At least 2 minutes were allowed to elapse between the disappearance of the contrast effect and

injection of the next dose of study agent. The first pre-injection echocardiogram had to confirm suboptimal EBD in the LV. The echocardiographic imaging was recorded on VHS tape.

The primary efficacy endpoint of the SonoVue studies (change from baseline in total LV EBD score) was prospectively defined and agreed upon with the FDA. The validity of improvement in EBD resulting from opacification of the LV as an aid in determination of more clinically relevant parameters is recognized by the 2008 ASE consensus statement that states: “The use of contrast agents for LVO improves the feasibility, accuracy, and reproducibility of echocardiography for the qualitative and quantitative assessment of LV structure and function at rest and during exercise or pharmacologic stress.”

The imaging protocols and MI ranges employed in the SonoVue confirmatory studies are representative of those still applicable using ultrasound equipment currently in place in echocardiography laboratories in the US and that are expected to continue to be used in the future. Although harmonic imaging for EBD was not available at the time the SonoVue EBD confirmatory studies were performed and thus was not included in the study methodology, it was evaluated later in two Bracco-sponsored SonoVue studies (BBG-001 and BBG-012) and in other studies reported in the literature. All these studies showed an improvement in image quality and EBD with SonoVue-enhanced echocardiography over that with unenhanced echocardiography performed with harmonic imaging. In addition, the ultrasound systems used in the SonoVue confirmatory studies, namely Acuson, Hewlett Packard, ATL, and Toshiba, are still the most widely used systems in routine clinical practice in the US. Imaging evaluation was conducted by experienced unaffiliated echocardiographers using prospectively defined methodology and was overseen by an independent core laboratory.

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).

Studies 019A & 019B

Studies BR1-019A and BR1-019B were identically designed studies with randomized, single blind (patient-blinded), parallel-group comparisons of SonoVue and Albunex, with a within group crossover dose-ranging design. 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.

The primary objectives of the studies BR1-019A and BR1-019B were:

1. To determine the optimal efficacious dose for SonoVue based on:
   - Left ventricle (LV) endocardial border delineation
   - LV opacification and duration of useful contrast enhancement.
2. To compare the efficacy profile of the SonoVue dose regimen to the Albunex dose regimen based on:
   - LV endocardial border delineation (used for determination of sample size)
   - LV opacification and duration of useful contrast enhancement.
3. To compare the safety profile of SonoVue (total dose up to 7.5 mL) to Albunex (Total dose up to 30 mL/kg).

The secondary objective of the studies was to compare the efficacy profile of the SonoVue dose regimen to the Albunex dose regimen based on:

- Duration of contrast shadowing and duration of total contrast effect
- Increase in diagnostic confidence, additional diagnostic information
- Patient management characteristics

Inclusion Criteria

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

Exclusion Criteria - Major

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

Four Doses SonoVue or Control

SonoVue Doses	Control Doses
0.5 ml	0.08 ml/kg Albunex
1.0 ml	0.22 ml/kg Albunex
2.0 ml	0.08 ml/kg Saline
4.0 ml	0.22 ml/kg Saline

Study 013

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.

The primary objective of the study BR1-013 was to compare the efficacy profile of two SonoVue doses (1 mL and 2 mL) based on LV endocardial border delineation.

The secondary objectives were:

1. To compare the efficacy profile of two SonoVue doses to each other and to the Albunex dose based on:
   (a) LV opacification and duration of useful contrast enhancement, duration of contrast shadowing, and total duration of contrast effect
   (b) Wall motion evaluation
   (c) Diagnosis including diagnostic confidence and additional diagnostic information
2. Patient management characteristics.
3. To compare the efficacy profile of two SonoVue doses to each other and to the Albunex dose to radionuclide ventriculography based on ejection fraction.
4. Monitor the safety profile SonoVue (total dose 3.0 mL) to Albunex (total dose 0.22 mL/kg).

Inclusion Criteria

Suspected cardiac disease (≥18 years age)
Suboptimal LV EBD (none-contrast ECHO)
Minimum EBD score ≥ 4/12 regions
Total EBD score ≤ 14/24
EF Radio nuclide ventriculography (RVG)
performed (14D prior – 2D post ECHO)

Exclusion Criteria - Major

Severe CHF
Recent myocardial infarction

Unstable angina
Serious arrhythmia
Severe pulmonary hypertension
Known hypersensitivity
Pregnant or lactating

All 3 Doses SonoVue and Control

SonoVue Doses	Control Dose
1.0 ml	0.22 ml/kg Albunex
2.2 ml	

Image Review Methods - Blinded Off-Site Reads

On-site Evaluation
Preinjection and postinjection echocardiographic images for each patient were evaluated by an experienced on-site echocardiographer, either the principal investigator or a co-investigator.

Off-site Evaluation
The blinded reads were conducted according to a prospectively defined methodology and were overseen by an independent core laboratory, which has been audited by the FDA at the time of the review of the original NDA submission with a positive outcome.

Pre-injection and post-injection echocardiographic images for each patient were evaluated by two off-site blinded, independent echocardiographers unaffiliated with any of the investigational sites of the study. The off-site readers for study BR1-019A were investigators participating in study BR1-019B and, conversely, the off-site readers for study BR1-019B were investigators participating in BR1-019A. The off-site readers for study BR1-013 had not previously participated in any clinical trials with SonoVue. A different set of blinded readers was used for each of the 3 confirmatory studies. All blinded readers were board certified in their respective fields of expertise.

All blinded reads followed a prospectively designed blinded read methodology. These were state-of-the-art echocardiograph imaging protocols for both unenhanced and contrast-enhanced images. Each off-site reader interpreted all images in the study. Each reader reviewed the first imaging session (first injection) for all patients first, followed by the second, third, and fourth sessions.

Images were reviewed in pairs; for a given injection number and patient, the patient's baseline images (collected prior to each injection) were reviewed first, immediately followed by a review of the patient's corresponding post-injection images. To insure that the reader did not review image pairs in the same patient order for each of the four

sessions, the order of presentation of patient videotapes to the off-site reviewers was determined by a randomization schedule generated for each of the sessions.

Studies 019A and 019B

The 2 Investigators from each study performed the blind reads for the other study Images were presented in pairs with knowledge of Pre- & post-injection time points Image pairs - presented by randomization - four sets.

Study 013

The 2 different & non-prior participant blinded readers performed these blind study reads. Images were presented in pairs with knowledge of Pre- & post-injection time points Image pairs - presented by randomization - three sets.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Proposed Indication:
"SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation"

Over the past decades, there has been an enormous increase in the use of echocardiography in the routine assessment of patients with suspected or known CAD. Echocardiography has a number of advantages compared with other techniques. Specifically, it is portable, noninvasive, and does not expose the patient to ionizing radiation. Echocardiography allows accurate assessment of regional and global left ventricular (LV) function and structure which is pivotal in the clinical management of patients with suspected CAD. Echocardiography can assess markers of LV function, such as LV ejection fraction, wall motion abnormalities, and systolic and end-diastolic volumes.

In order to perform these evaluations accurately, the single most important aspect of the echocardiographic examination is to clearly visualize the LV endocardial border, which provides the basis for qualitative and quantitative assessment of all LV function parameters. In patients with poor visualization of the endocardial border, either the ability to evaluate LV function is precluded or the operator confidence in the evaluation of LV function is reduced. Despite substantial technical improvements in image quality on the equipment side, approximately 30% of patients continue to undergo echocardiographic examinations including stress tests that are non-diagnostic or

inconclusive due to poor image quality, with subsequent poor evaluation of cardiac function, leading to the need for more invasive techniques. These patients would benefit from a contrast agent that can opacify the LV and improve the delineation of endocardial borders.

In contrast-enhanced echocardiography, the degree of LV opacification (LVO) and duration of useful contrast effect are important measures since they can affect the quality of endocardial border delineation (EBD) and the number of visualized cardiac segments. Prolonged and persistent LVO is also important for a complete evaluation of the LV to ensure sufficient time for image acquisition from multiple cross-sectional views.

In the three confirmatory studies BR1-019A, BR1-019B, and BR-013, the administration of SonoVue in 317 patients resulted in:

- significant increase of EBD scores when compared to baseline unenhanced echocardiography and to controls (saline or Albunex). The mean change from baseline scores after SonoVue administration ranged from 3.6 to 18.2, whereas an increase of total EBD score from baseline of ≥4 was observed in 42% to 98% of patients.

- a higher percentage of patients who converted from suboptimal to adequate image quality. A marked reduction in the proportion of patients with inadequate EBD in ≥1 segment, ≥2 segments, ≥2 adjacent segments, and in at least 1 or 2 critical segments could be observed with SonoVue.

- a higher percentage of patients (73% to 93% across all off-site readers and across all SonoVue doses) with LVO scores of +2 or +3 when compared to patients in the control groups (range between 28% and 46%).

- greater mean duration of useful contrast when compared to the highest dose of the comparator. The duration of useful contrast was dose-dependent and ranged from 1 minute to 4 minutes.

In 1 of the 2 supportive multicenter clinical trials, similar increases in EBD score were observed when SonoVue was administered for echocardiography performed at rest and during pharmacological stress.

The effectiveness and suitability of SonoVue as a contrast agent for use with echocardiography to obtain left ventricular opacification and improve endocardial border delineation have been demonstrated. Clinical studies have also shown SonoVue to be safe and well tolerated with minimal risk to patients.

6.1.1 Methods

To support the use of SonoVue in echocardiography to obtain left ventricular opacification and improve endocardial border delineation, a program of clinical studies have been conducted with the following aims:

- to determine the optimal dose of SonoVue for endocardial border delineation through the provision of adequate and prolonged opacification of the left ventricular cavity;
- to compare the diagnostic performance of SonoVue to that of a control agent (Albunex and/or saline) in the delineation of the ventricular border;
- to evaluate the effectiveness of SonoVue in improving the delineation of the endocardial border in patients with suspected cardiac disease and suboptimal unenhanced echocardiography.

Endocardial Border Delineation Score

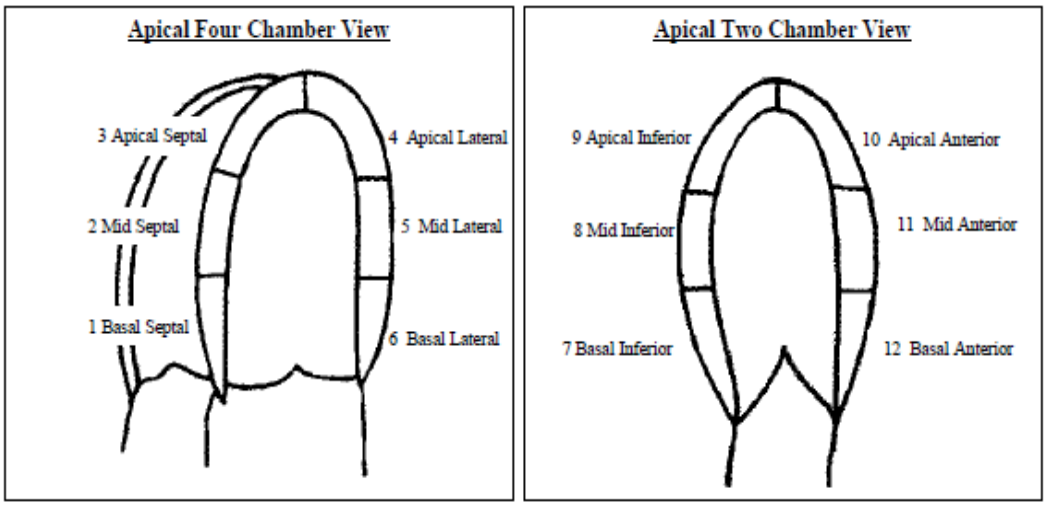
The EBD score was based on 6 segments only, either apical two-chamber or four-chamber view. A total delineation score (EBD 0-24) obtained by adding the scores from the 6 individual segments in each of two views, the apical four-chamber view and apical two-chamber views.

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 United States and abroad. A total delineation score (0-24) was obtained by adding the scores from the 6 individual segments in each of two views, the apical four-chamber and apical two-chamber views (**Figure 4**).

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)

Figure 4 : Apical Four-Chamber and Two-Chamber Views for Assessment of EBD and LVO in Studies BR1-019A, BR1-019B and BR1-013



Left Ventricle Opacification Score

Degree of left ventricle opacification following each injection 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.

For duration of contrast effect: time taken from the first weak (+1) appearance of contrast within the left ventricular cavity until it had virtually disappeared (<+1).
The flow pattern of SonoVue in the left ventricle was to be provided in descriptive terms.

Endpoints Related to Assessment of Ventricular Function

Ejection Fraction (BR1-013 only)

Ejection fraction was calculated from pre-injection and post-injection echocardiographic images for each dose of study agent. Measurements were obtained on-site and off-site (in the centralized, blinded evaluation). Ejection fraction measurements from echocardiographic images were compared with those obtained from radionuclide ventriculography, which was performed on-site. Ejection fraction measurements were obtained from the off-site evaluation of echocardiographic images using three methods:

1) original central laboratory calculation using biplane method of disks; 2) calculation, based on a reread of images by an independent reader using the 4-chamber method of disks; and 3) global assessment based on these calculated values (4-chamber method of disks) and clinical assessment of videotaped images.

Left ventricular volumes were calculated from echocardiographic images using the biplane method of discs (modified Simpson's rule) or 4-chamber method of disks, as described above, and left ventricle ejection fraction was calculated as follows:

$$\text{Ejection fraction (\%)} = \frac{\text{(End-diastolic volume) - (End-systolic volume)}}{\text{(End-diastolic volume)}} \times 100$$

Ejection fraction measurements obtained from RVG were calculated using the count volume or time-activity method (gated equilibrium blood pool). Left ventricle ejection fraction was calculated as follows:

$$\text{Ejection fraction (\%)} = \frac{\text{(End-diastolic counts) - (End-systolic counts)}}{\text{(End-diastolic counts) – background counts}} \times 100$$

Wall Motion Evaluation

Wall motion was evaluated from preinjection and postinjection images for each of the six segments as seen on the apical 2-chamber and 4-chamber views and graded according to the following six-point rating scale:

0 = Uncertain
1 = Normal
2 = Hypokinetic
3 = Akinetic
4 = Dyskinetic
5 = Aneurysmal

Endpoint Assessments

The primary efficacy endpoint of the SonoVue studies (change from baseline in total left ventricle EBD score) was prospectively defined and mirrors that adopted in registration studies by ultrasound contrast agents currently approved in the United States for echocardiography. The validity of improvement in EBD resulting from opacification of the left ventricle as an aid in determination of more clinically relevant parameters is recognized by the 2008 ASE consensus statement that states: "The use of contrast agents for left ventricular opacification (LVO) improves the feasibility, accuracy, and

reproducibility of echocardiography for the qualitative and quantitative assessment of LV structure and function at rest and during exercise or pharmacologic stress."

Primary Diagnosis and Confidence in Primary Diagnosis

Pre-injection and post-injection images were evaluated (on-site and off-site) for diagnostic findings. For diagnostic findings, the reader selected one or more from the following categories:

- None
- Wall Motion Abnormality (global or regional);
  - if Global, mild, moderate, severe, or uncertain could be selected
  - if Regional, type and location of regional wall motion abnormality could be selected. Multiple anatomical regions could be selected, but a single type of anomaly for each anatomical region must be specified.
- Valvular Abnormality: Multiple anatomical regions could be selected, but a single type of anomaly for each anatomical region must be specified.
- Chamber Abnormality: Multiple anatomical regions could be selected, but a single type of anomaly for each anatomical region must be specified. Atrium enlargement did not require any further clarification of anomaly.
- Cardiac Wall Hypertrophy.
- Normal: No abnormalities seen.

Confidence in primary diagnosis: For those images rated as diagnostic, the primary diagnosis was recorded together with the reader's overall confidence in the primary diagnosis rated on a scale from 1 (low confidence) to 5 (high confidence).

6.1.2 Demographics

The study populations in the three confirmatory studies were comprised of male and female patients, ≥18 years of age, with suspected cardiac disease and suboptimal border delineation on unenhanced 2D transthoracic echocardiography at rest. In order to verify that the patient had suboptimal left ventricular endocardial border delineation, unenhanced 2D transthoracic echocardiographic imaging of the apical four- and two-chamber views was performed within 7 days prior to contrast imaging. Suboptimal was defined as a total border delineation score not greater than 14 (out of 24) from the apical 2-chamber and apical 4-chamber views combined; however, patients were required to have a minimum of 4 segments (out of 12) with sufficient or good visibility (ie, a delineation rating of +1 or +2). In addition, patients enrolled in study BR1-013 were also to have RVG performed within 14 days prior to or 2 days after study agent administration for determination of EF. The requirement for patients to have suboptimal border delineation on unenhanced echocardiography was dictated by the approved indication for Albunex as stated in the package insert.

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). Twenty-eight percent (28%) of patients who received SonoVue and 34% of patients who received control had NYHA Class II/III heart disease. For subjects in study BR1-013, the mean ejection fraction was 46.5% (range: 10% to 66%)(**Table 3**)

Table 3 : Demographic and Baseline Characteristics in Confirmatory Studies for Endocardial Border Delineation by Study

	BR1-019A		BR1-019B		BR1-013[b]
Parameter	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.

In the 3 confirmatory studies, all study agent doses were administered as single intravenous bolus injections. At least 2 minutes elapsed between the disappearance of

contrast effect and the next injection of study agent. A recording of 2D echocardiography was obtained from 30 seconds prior to each injection of study agent (baseline) to at least 15 minutes after dosing or until the disappearance of the contrast effect (return to baseline), whichever was longer.

6.1.3 Subject Disposition

The up-dated number of subjects randomized, who received at least one dose of study drug, completed study, or were prematurely discontinued, and the reason for discontinuance is summarized in **Table 26**.

6.1.4 Analysis of Primary Endpoint(s)

Overall Efficacy Conclusions

The results of EBD score, degree of LVO, and duration of useful contrast, summarized together, suggest that optimal contrast images can be obtained with the 2-mL SonoVue dose. Degree of LVO and duration of useful contrast effect after administration of a contrast agent are important measures of contrast enhancement in echocardiography since they can affect the quality of EBD and the number of visualized cardiac segments. Prolonged and persistent LVO is also important for a complete evaluation of the LV to ensure sufficient time for image acquisition from multiple cross-sectional views. The duration of a contrast-enhanced echocardiographic study is dependent on a number of factors. A study can be shorter if performed by an experienced versus an inexperienced sonographer and in a patient with easier obtainable acoustic windows. The duration of a contrast-enhanced echocardiographic study is also dependent on the indications of the study (e.g. exclusion of LV thrombus, evaluation of LV function, evaluate source of chest pain, rest only or rest and stress study, etc.). For evaluation of LV function, a number of cardiac cycles per each view may be required. Therefore, following one dose of contrast agent, the useful contrast effect should last at least 2 to 3 minutes to ensure a successful and complete evaluation.

In the confirmatory studies, analysis of all efficacy endpoints was performed for the intent-to-treat (ITT) population, which included all patients who had received at least one dose of study agent and who had any efficacy data collected (i.e., at least one post-injection evaluation, or both baseline and at least one post-injection evaluation for change from baseline values). Patient data were grouped and summarized according to the dosing groups assigned through randomization (i.e., “as randomized”).

In general, summary statistics (N, mean, median, standard deviation [SD], and range) were provided for continuous variables and the number and percentage of patients in each category were provided for categorical data (e.g., opacification score or overall confidence in primary diagnosis). Statistical significance was defined as $p<0.05$ (two-tailed) for all studies. In study BR1-013, within each of the three separate reader

analyses (i.e., on-site reader and two off-site readers), statistical significance for the endocardial border delineation analysis was defined as p<0.025 (two-tailed) to adjust for the multiple comparisons of each dose of SonoVue vs control. Otherwise, no adjustments were made for multiple comparisons.

Visualization of the Endocardial Border

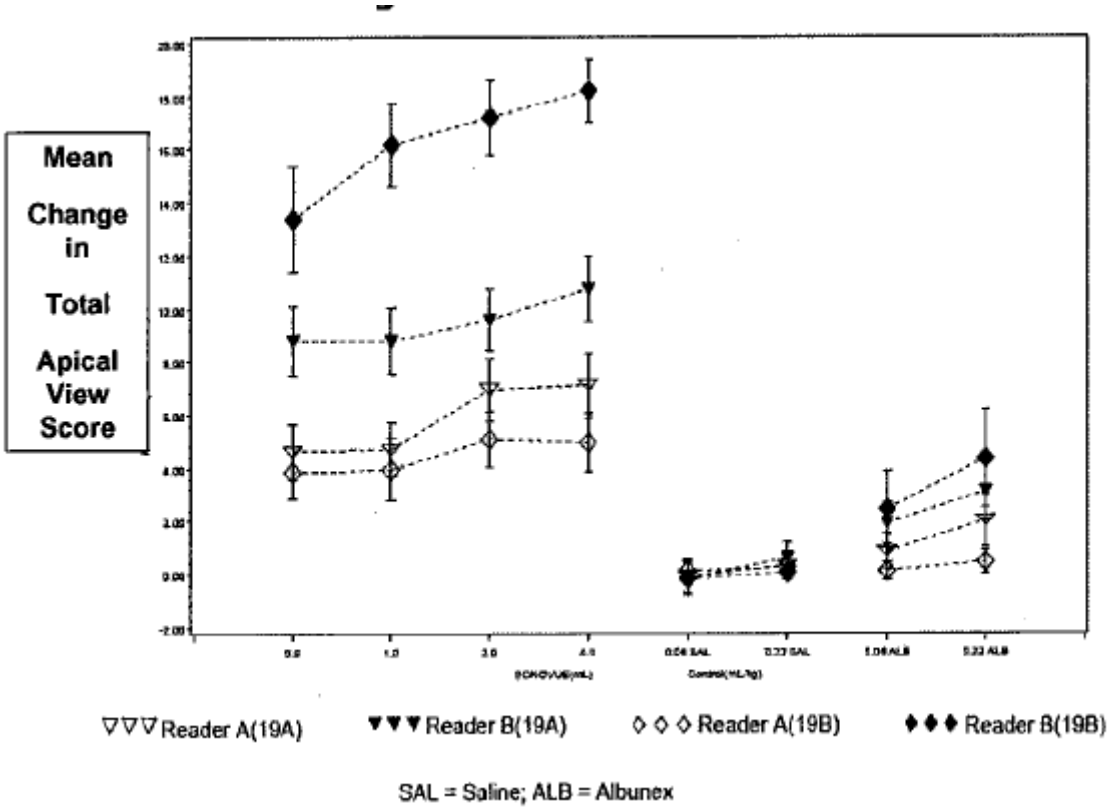
In the three confirmatory studies BR1-019A, BR1-019B, and BR-013, EBD significantly improved with SonoVue when compared to baseline unenhanced echocardiography and to controls (saline or Albunex). Across all off-site readers and across the four SonoVue tested doses, the mean change from baseline scores after SonoVue administration ranged from 3.6 to 18.2 and these changes were statistically significant. In addition, an increase of total LV EBD score from baseline of ≥4 was observed in 42% to 98% of patients for the SonoVue dose groups compared with 0% to 38% across the control dose groups (saline and Albunex) (**Table 4**)

Table 4 : Mean Change Baseline (Pre-Injection) to Post-Injection Total LV EBD 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	--	--	--

Figure 5 displays the mean change in total apical view left ventricular EBD score by readers from baseline to post-injection. While the inter- reader pre-contrast performance with Sonovue (left side of figure) is dissimilar, the post-injection changes are significantly improved. The right side of the figure displays the minimal improvement shown by the controls.

Figure 5 : 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



The percentage of patients with at least one segment with inadequate border delineation (segment score of zero) is summarized in **Table 5** for all SonoVue dose groups in the confirmatory studies (4-chamber view). In studies BR1-019A and -019B, the percentage of patients with inadequate border delineation in at least one segment decreased as the SonoVue dose increased. At the higher SonoVue doses (2 mL and 4 mL), the percentage of patients with inadequate border delineation in at least one segment post-injection ranged from 8% to 28%. Thus, 72% to 92% of patients in these groups had all segments visualized.

In contrast, the percentage of patients with inadequate border delineation in at least one segment ranged from 64% to 98% for saline (only 2% to 36% with all segments visualized), and from 58% to 83% for Albunex (17% to 42% with all segments visualized). For all doses of SonoVue, a reduction in the percentage of patients with inadequate border delineation was observed for the majority of individual segments in both the apical 4-chamber and apical 2-chamber views.

Table 5 : Percentage of Patients With Inadequate Border Delineation in at Least One Segment (Apical 4-Chamber View) All SonoVue Dose Groups in Studies Off-site Image Evaluation

	BR1-019A		BR1-019B		BR1-013	
SonoVue Dose (mL)	Preinjection (%)	Postinjection (%)	Preinjection (%)	Postinjection (%)	Preinjection (%)	Postinjection (%)
Reader A[a]						
0.5	88.2	44.7	69.4	40.3	---	---
1.0	89.5	38.2	64.5	37.1	15.1	1.9
2.0	88.2	19.7	61.3	24.2	20.8	13.2
4.0	85.5	27.6	61.3	25.8	---	---
Reader B[a]						
0.5	92.1	36.8	95.2	25.8	---	---
1.0	89.5	28.9	95.2	8.1	84.9	45.3
2.0	90.8	27.6	95.2	9.7	90.6	35.8
4.0	86.8	27.6	95.2	8.1	---	---

Segment score of 0 = Inadequate (border not visible)
a Represents different individuals in each of the 3 studies.

Left Ventricle Opacification Scores

In studies BR1-019A and BR1-019B, the percentage of patients with LVO scores of +2 or +3 (moderate or complete opacification) ranged from 73% to 93% across all off-site readers and across all SonoVue doses, higher than the percentage of patients in the control groups (range between 28% and 46%) who had a maximum response (defined as the maximum score, including -1 through +3, for each patient among the dose groups for the controls).

As observed for assessment of EBD, a clear dose-response effect was evident for degree of LVO. However, the difference among the four SonoVue doses in terms of percentage of patients with LVO scores of +2 or +3 was greater when doses increased from 0.5 mL to 2 mL than when doses increased from the 2-mL to the 4-mL doses, at least for 3 of the 4 off-site readers (**Table 6** and **Table 7**)

Table 6 : Percentage Patients with LV Opacification Maximal Scores +2 (Moderate) or +3 (Maximal)

	Study BR1-019A			Study BR1-019B			Study BR1-013		
Reader A	N	Score +2 or +3	Score +3	N	Score +2 or +3	Score +3	N	Score +2 or +3	Score +3
Dose 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%			
Reader B									
Dose 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%			

Opacification scores +2 or +3 = > 70% all patients
Opacification scores +2 or +3 = > 80% patients in 2 mL & 4 mL groups

Table 7 : Left Ventricular Opacification Scores Post 2.0-mL Dose of SonoVue

	Nb	Non-Diagnostic	N (%) of Patients with LV Opacification Score			
		-1 n (%)	0 n (%)	+1 n (%)	+2 n (%)	+3 n (%)
Study A (019A)						
Reader 1	76	7 (9)	0	3 (4)	5 (7)	61 (80)
Reader 2	76	3 (4)	0	8 (11)	22 (29)	43 (57)
Study B (019B)						
Reader 3	62	7 (11)	0	0	23 (37)	32 (52)
Reader 4	62	2 (3)	0	5 (8)	6 (10)	49 (79)
Study C (013)						
Reader 5	53	-	2 (3.8)	2 (3.8)	20 (38)	29 (55)
Reader 6	53	-	1 (1.9)	1 (1.9)	13 (25)	38 (72)

a The degree of left ventricle opacification after contrast agent administration was rated as follows:
-1 = Score assigned to non-diagnostic images (Study A and Study B only)
0=None (no visible contrast)
+1=Faint (weak, or trace effect of contrast within left ventricle)
+2=Moderate (some areas of the left ventricle fully opacified but without a time when the whole cavity is filled with contrast of the same high intensity)
+3=Complete (homogeneous, high intensity contrast effect)
b Includes patients who had postinjection image evaluations.

Clinical Trial Conclusions - 019A, 019B, & 013

- Significant increase of EBD scores when compared to baseline unenhanced echocardiography (and controls).

- Higher percentage of patients who converted from suboptimal to adequate image quality.

- Reduction in the proportion of patients with inadequate EBD in ≥1 segment, ≥2 segments, ≥2 adjacent segments, and in at least 1 or 2 critical segments (distal part of main branch coronary artery) could be observed with SonoVue.

- Higher percentage of patients with LVO scores of +2 or +3 when compared to patients in the control groups.

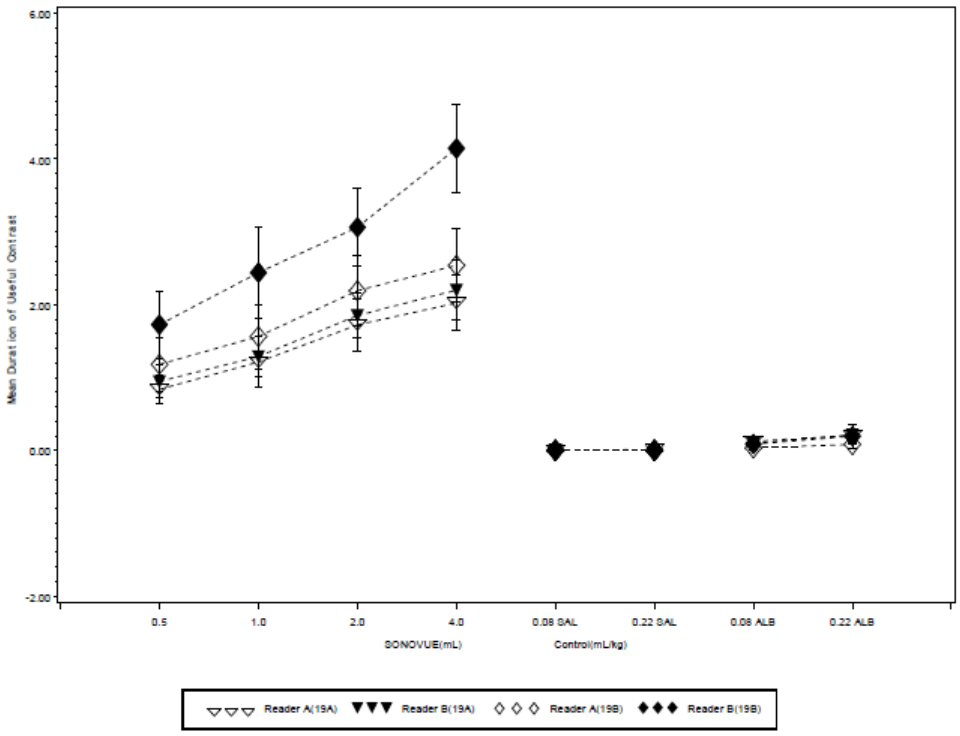
6.1.5 Analysis of Secondary Endpoints(s)

Duration of Useful Contrast

In studies BR1-019A and BR1-019B, the mean duration of useful contrast effect increased with increasing doses of SonoVue; >0.3 minutes increases in useful contrast duration were reported by the four readers for the 0.5- through 2.0-mL doses. In contrast, the difference in mean duration between the 2-mL and the 4-mL doses was greater than 0.3 minutes for only one of the 4 off-site readers. When data for the two studies are combined, there is no overlap between the 95% CIs for mean duration between the 1-mL dose and the 2-mL dose, indicating superiority of the 2-mL dose, while the 95% CIs for the 2-mL and 4 mL doses are overlapping.

At the highest SonoVue doses (2mL and 4 mL), the mean duration of useful contrast effect ranged from 1.7 to 4.1 minutes (**Figure 6**). No useful contrast effect was observed for the saline doses. For Albunex, even at the higher dose (0.22 mL/kg), the mean duration of useful contrast was less than 15 seconds.

Figure 6 : Mean Duration of Useful Contrast Effect by Study Agent, Off-site Image Evaluation in Confirmatory Studies BR1-019A and BR1-019B



Conversion of Total Apical EBD Score from Suboptimal (Score ≤10) to Adequate (≥14)

For each dose of the study agent, the total apical EBD score was derived for each patient by averaging over the total apical EBD scores from different readers. Based on those average scores, the number and percent of patients with a total apical EBD score of ≤10 pre-dose and ≥14 post-dose were presented for each dose of the study agent.

Logistic regression was employed to assess the overall dose effect, including terms for protocol and dose group. In addition, pair-wise comparisons of doses for the numbers and percentages of patients with ≤10 pre-dose and ≥14 post-dose were done, with 2-sided 95% CI presented. (**Table 8)**

Table 8 : Endocardial Border Delineation Score Conversion of Pre-dose Suboptimal Images (Total Apical View Score ≤10) to Diagnostic Images (Total Apical View Score >14) in Confirmatory Studies

Reader Study Agent Dose	BR1-019A N	BR1-019A Converted to Diagnostic n (%)	BR1-019B N	BR1-019B Converted to Diagnostic n (%)	BR1-013 N	BR1-013 Converted to Diagnostic n (%)
Reader A						
SonoVue (mL)						
0.5	60	19 (31.7)	40	9 (22.5)	--	--
1.0	57	13 (22.8)	38	6 (15.8)	13	1 (7.7)
2.0	55	26 (47.3)	41	14 (34.2)	14	2 (14.3)
4.0	59	23 (39.0)	40	13 (32.5)	--	--
Control (mL/kg)						
Saline 0.08	48	0	42	0	--	--
0.22	46	0	41	0	--	--
Albunex 0.08	48	0	41	0	--	--
0.22	50	5 (10.0)	40	0	13	0
Reader B						
SonoVue (mL)						
0.5	63	33 (52.4)	58	40 (69.0)	--	--
1.0	57	32 (56.1)	58	49 (84.5)	47	1 (2.1)
2.0	54	31 (57.4)	56	50 (89.3)	45	5 (11.1)
4.0	64	44 (68.8)	60	55 (91.7)	--	--
Control (mL/kg)						
Saline 0.08	46	0	58	0	--	--
0.22	50	0	58	0	--	--
Albunex 0.08	51	3 (5.9)	56	7 (12.5)	--	--
0.22	51	8 (15.7)	57	11 (19.3)	47	0
On-site						
SonoVue (mL)						
0.5	52	22 (42.3)	36	21 (58.3)	--	--
1.0	52	21 (40.4)	38	25 (65.8)	33	17 (51.5)
2.0	51	26 (51.0)	35	26 (74.3)	32	15 (46.9)
4.0	52	28 (53.9)	39	29 (74.4)	--	--
Control (mL/kg)						
Saline 0.08	50	0	38	0	--	--
0.22	53	1 (1.9)	39	0	--	--
Albunex 0.08	56	6 (10.7)	36	2 (5.6)	--	--
0.22	52	6 (11.5)	38	5 (13.2)	30	1 (3.3)

N represents the number of patients with suboptimal images prior to injection of study agent, as defined by an EBD score of ≤ 10.

This analysis confirms the efficacy of SonoVue at improving the EBD. The use of SonoVue markedly decreased the proportion of patients with suboptimal images that converted to diagnostic images. In Studies 019A and 019B, the 2 mL dose converted 34%-89% (depending on reader) of 95 -110 suboptimal images (Total Apical View Score ≤10) to diagnostic images (Total Apical View Score >14).

Conversion of EBD Score from Inadequate to Adequate *in* ≥2 *Segments*

For each dose of the study agent, the total number of segments with inadequate EBD score for each patient was derived by averaging over the total number of segments with inadequate EBD score from different readers. Shift tables were then provided for patients with at least two segments with inadequate EBD, pre-dose versus post-dose by dose of the study agent. In addition, logistic regression was employed to assess the overall dose effect, including terms for protocol and dose group.

Primary Diagnosis and Confidence in Primary Diagnosis
Changes in primary diagnosis from pre-injection to post-injection were summarized descriptively for each dose of study agent. In studies BR1-019A and -019B, between-group differences in change from baseline in overall confidence score were analyzed using an ANCOVA model with terms for site, study agent group, and baseline score as covariate. In study BR1-013, paired differences were analyzed using the Wilcoxon signed-rank test.

Diagnostic Conversion Rates

Diagnostic Conversion Based on Inadequate Endocardial Border Delineation in Adjacent Segments

A significant proportion of patients with inadequate EBD in ≥2 adjacent segments, and in at least 1 and 2 critical segments converted to adequate image quality with SonoVue. The efficiency of SonoVue for EBD improvement, when compared with controls, was also confirmed by the results of additional analyses showing that a higher percentage of patients converted from suboptimal to adequate image quality with SonoVue. Visualization of adjacent endocardial border segments contributes important clinical information. When the adjacent segments belong to the same perfusion territory, it can provide information about the extent of myocardial ischemia or viability in patients with ischemic heart disease. Deterioration of wall motion of two adjacent segments during stress echocardiography is utilized as a definition of an ischemic response in both clinical studies as well as clinical practice.

Table 9 presents the proportion of patients with inadequate border delineation in at least one pair of adjacent segments with the 2 mL dose for Studies BR1-019A, BR1-019B and BR1-013 and the percentage of patients with decrease in inadequate border delineation post SonoVue. SonoVue markedly decreased the proportion of patients with inadequate border delineation in at least one pair of adjacent segments; the proportion of patients decreased more with the use of SonoVue than for controls (Albunex and saline). For the 2 mL dose, the off-site reader's results (except for Reader A in Study BR1-013) showed 31% to 77% decreases in the proportion of patients with inadequate border delineation in at least one pair of adjacent segments post administration of SonoVue.

Table 9 : Patients with Inadequate Border Delineation in Combined View in at Least One Pair of Adjacent Segments in Confirmatory Studies at 2.0 mL Dose

Readers	BR1-019A		BR1-019B		BR1-013	
	Pre-Dose N (%)	Post-Dose N (%)	Pre-Dose N (%)	Post-Dose N (%)	Pre-Dose N (%)	Post-Dose N (%)
A	60 (79)	25 (33)	31 (50)	12 (19)	12 (23)	10 (19)
	46 % Decrease		31 % Decrease		4 % Decrease	
B	62 (82)	28 (37)	54 (87)	6 (10)	45 (85)	20 (38)
	45 % Decrease		77 % Decrease		47 % Decrease	

Table 10 presents the off-site reader's results (except for Reader A in Study BR1-013) and shows that 55% to 89% converted to adequate image quality post administration of SonoVue.

Table 10 : Diagnostic Conversion Rates After Treatment of Patients with Suboptimal Images at Baseline in Confirmatory Studies Patients with inadequate EBD score in at least 2 Adjacent Segments at Baseline (score 0) Converted to Adequate EBD Post-dose (Score 1=sufficient or 2=good) Combined View

	SonoView 2.0 mL		
	Patients Treated N	Patients with Inadequate Image Quality	Patients Converted to Adequate Image Quality
BR-019A			
Reader A	76	60	35 (58%)
Reader B	76	62	34 (55%)
BR-019B			
Reader A	62	31	19 (61%)
Reader B	62	54	48 (89%)
BR-013			
Reader A	53	12	2 (17%)
Reader B	53	45	25 (56%)

Diagnostic Conversion Based on Inadequate Endocardial Border Delineation of Critical Segments

Although each of the 12 segments analyzed in the 2- and 4-chamber apical views are important in making a diagnosis, 6 segments representing the distal supply territory of the main coronary arteries are essential in order to obtain clinically accurate information. The definition of a critical segment is based on the fact that every coronary artery

supplies a part of the myocardium that is distal to it, and some of the segments embody the most distal part of the arteries supplied territory. That is to say that the normality, or abnormality, of that region can by itself be indicative of whether the coronary artery is normal or not. For example, in the apical four chamber view, if the apical septum is normal then it is very unlikely that there is left artery disease (LAD) because the apical septum represents the most distal part of the LAD territory.

Each standard apical view of the left ventricle has critical segments representative of the perfusion territory of the distal part of coronary artery main branches, i.e., in the apical four chamber view:

- the apical septal segment represents left anterior descending distribution;
- the mid lateral segment represents left circumflex distribution;
- the apical lateral segment represents left anterior descending and circumflex distribution, and, in the apical two-chamber view:
- the apical anterior segment represents left anterior descending distribution;
- the mid inferior segment represents right coronary distribution;
- the basal inferior segment represents right coronary distribution.

The inability to visualize these critical segments may render the study non-diagnostic and a patient may be referred to another imaging modality. The six endocardial border segments noted above were identified as the most important to visualize by an expert panel of cardiologists convened by Bracco Diagnostics to assess the concept of critical segments in the clinical practice of echocardiography.

Patients with inadequate border delineation in at least one critical segment are presented for pre-dose and post-dose in **Table 11**, for studies BR1-019A, BR1-019B, and BR1-013.

The use of SonoVue markedly decreased the proportion of patients with inadequate border delineation scores in at least one critical segment. The proportion of patients decreased more with the use of SonoVue than for control (Albunex or saline). The effects at the 2-mL dose and 4-mL dose were comparable. For the 2-mL dose in studies study BR1-019A and -019B, the onsite results and the off-site results showed marked absolute decreases in the percentage of patients with inadequate border delineation in at least one critical segment ranging from 36% (Reader A – study BR1-019B: from 63% to 27%) to 82% (Reader B - study BR1-019B: from 92% to 10%). For study BR1-013, similar absolute decreases in these percentages were observed. For Albunex (0.22 mL/kg), the maximum decrease observed was 25% (study BR1-013 - on-site: from 77% to 53%).

Table 11 : Patients with Inadequate Border Delineation in at Least One Critical Segment in Confirmatory Studies BR1-019A, BR1-019B, and BR1-013

At least 1 Critical Segment	SonoVue 2.0 mL Dose	
	Pre-dose n (%)	Post-dose n (%)
BR-019A		
Reader A	65 (86%)	28 (37%)
Reader B	65 (86%)	31 (41%)
BR-019B		
Reader A	39 (63%)	17 (27%)
Reader B	57 (92%)	6 (10%)
BR-013		
Reader A	11 (21%)	10 (19%)
Reader B	48 (91%)	26 (49%)

The conversion rate for the 2-mL dose ranged from 52% and 89% among the off-site readers in studies BR1-019A and BR1-019B. Baseline echocardiography showed inadequate EBD in at least one critical segment in 86%, 86%, 63% and 92% across all readers at baseline, with a decrease to 37%, 41%, 27% and 10% after administration of 2-mL SonoVue. In study BR1-013 conversion rates were 2% for Reader A and 46% for Reader B.

Patients with inadequate border delineation in at least two critical segments are presented for pre-dose and post-dose in **Table 12**, for studies BR1-019A, BR1-019B, and BR1-013. A significant proportion of patients with inadequate EBD in at least 2 critical segments converted to adequate image quality with SonoVue.

Table 12 : Diagnostic Conversion Rates After Treatment of Patients with Suboptimal Images at Baseline in Confirmatory Studies Patients with inadequate EBD score in at least 2 Critical Segments at Baseline (score 0) Converted to Adequate EBD Post-dose (score 1=sufficient or 2=good)

At least 2 Critical Segments	SonoVue 2.0 mL Dose	
	Pre-dose n (%)	Post-dose n (%)
BR-019A		
Reader A	51 (67%)	19 (25%)
Reader B	49 (65%)	18 (24%)
BR-019B		
Reader A	24 (39%)	13 (21%)
Reader B	51 (82%)	4 (7%)
BR-013		
Reader A	6 (11%)	5 (9%)
Reader B	42 (79%)	12 (23%)

The use of SonoVue also decreased the proportion of patients with inadequate border delineation scores in at least two critical segments, with the proportion of patients with decreases greater for SonoVue than for control (Albunex or saline). The effects at 2-mL dose and 4-mL dose were comparable. For the 2-mL dose, the on-site results and the off-site results (except for Reader A in study BR1-013) showed marked absolute decreases in the percentage of patients with inadequate border delineation in at least two critical segment ranging from 18% (Reader A – study BR1-019B: from 39% to 21%) to 75% (Reader B – study BR1-019B: from 82% to 7%). For Albunex (0.22 mL/kg), the maximum decrease observed was 24% (study BR1-019A - on-site: from 73% to 49%).

Diagnostic Performance - Ejection Fraction - Study 013

In study BR1-013, ejection fraction was derived from pre-injection and post-injection echocardiographic images and summarized descriptively for each of the three treatments. For each treatment, comparison of ejection fractions obtained from radionuclide ventriculography with that obtained from each of the three methods of analysis of echocardiographic images was performed by means of a plot of the difference in ejection fraction against the mean of the ejection fractions as describeed by Bland and Altman. In addition, correlation coefficients between ejection fractions were obtained from pre- and post-injection echocardiographic images (**Table 13**).

Table 13 : Ejection Fraction Correlation Between ECHO & RV - Off-site Image Evaluation

Study Agent	Dose	Timepoint	Reader Global Assessment
SonoVue	2.0 mL	Preinjection	0.66
		Postinjection	0.76

Correlation based on Pearson's correlation coefficient

Diagnostic Performance - Accuracy in Segmental Wall Motion Assessment - Study 013

In study BR1-013, in order to assess the accuracy of unenhanced ultrasound imaging and SonoVue-enhanced imaging in segmental wall motion assessment, the imaging results were compared with results from RVG. The assessment of regional wall motion (normal, abnormal, uncertain) for pre-dose and each of the three doses were analyzed. Regional contraction abnormalities included findings of akinesis (absence of systolic contraction), hypokinesis (reduced systolic contraction), or dyskinesis (systolic thinning or bulging). Presence of regional wall motion abnormality was summarized using the following categories: non-diagnostic assessment, no regional wall motion abnormalities detected, regional wall motion abnormality detected. Accuracy, sensitivity, and specificity for detection of regional wall motion abnormality for each reader were presented.

Wall motion abnormalities for each segment were graded on a 6-point scale (0 to 5) were further mapped to a 2-point scale: 0 = uncertain (for segment score of 0) and 1 = not uncertain (for segment scores of 1, 2, 3, 4, or 5). The change from baseline in total wall motion score for each patient (i.e., number of segments for which wall motion was not uncertain, 0 to 12) was summarized descriptively and tested using an ANCOVA model with terms for patient, injection number, treatment, and baseline score (number of segments not uncertain at baseline) as covariate. The results confirm that even with contrast echocardiography, detection of wall motion has its limitations (**Table 14**).

Table 14 : ECHO Compared to Radionuclide-Ventriculography (RV) for Detection of Wall Motion Abnormality

	SonoView 2.0 mL	
	Pre-dose	Post-dose
	Sensitivity for Detection of Regional Wall Motion Abnormality (N=17) +	
Reader A	4 (24%)	4 (24%)
Reader B	4 (24%)	7 (41%)
	Specificity for Detection of Regional Wall Motion Abnormality (N=36)*	
Reader A	30 (83%)	30 (83%)
Reader B	13 (36%)	22 (61%)

+ Number (%) of patients with abnormalities identified by ECHO as compared with RVG

* Number (%) of patients with no abnormalities identified by ECHO as compared with RVG

6.1.6 Other Endpoints

There are no additional endpoints.

6.1.7 Subpopulations

The following tables compare the changes from baseline in the left ventricular endocardial border total apical view scores following administration of the 2 mL proposed SonoVue dose and the largest control dose by age (**Table 15)** and gender groups(**Table 16)** in Studies 019A, 019B & 013. Neither age nor gender demonstrated any impact on the post-injection results.

Table 15 : Left Ventricle Endocardial Border Delineation Change from BaselineTotal Apical View Score by Age Group – Studies 019A, 019B & 013

Age Group	Dose	Number Patients	Post-Injection Mean Increase
18-64	SonoVue 2.0 mL	118	8.9
	Saline 0.22 mL/kg	76	0.3
≥65	SonoVue 2.0 mL	73	6.7
	Saline 0.22 mL/kg	49	0.3

Table 16 : Left Ventricle Endocardial Border Delineation Change from Baseline Total Apical View Score by Gender – Studies 019A, 019B & 013

Gender Group	Dose	Number Patients	Post-Injection Mean Increase
Male	**SonoVue 2.0 mL**	127	8.0
	Saline 0.22 mL/kg	90	0.1
Female	**SonoVue 2.0 mL**	64	8.1
	Saline 0.22 mL/kg	35	1.0

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the results from all studies (demonstrated in most Tables in this document), the useful contrast effect and endocardial delineation scores increased with increasing doses of SonoVue from the 0.05 mL through the 2.0 mL dose. However, the 4.0 mL highest dose evaluated did not demonstrate any advantage over the 2.0 mL dose. Therefore, we agree with the choice of the 2 mL dose as the dose selected for marketing

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Microsphere persistence of efficacy is limited to echocardiographic examination during the 2 or more minutes they circulate within the vascular system post administration before the microspheres self destruct. If necessary to complete the examination, a second dose can be administered.

Tolerance effects are not anticipated.

6.1.10 Additional Efficacy Issues/Analyses

All efficacy issues and analyses have been provided in this document.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical trial data for adverse events (including fatal cases) are derived from Bracco's clinical trial safety database for completed trials and from information provided to Bracco for ongoing studies. In total, to date 6723 patients have been dosed with SonoVue in clinical trials.

The current Bracco clinical trial safety database contains pooled data from 70 clinical trials conducted (62 in patients and 8 in healthy volunteers), during which 5275 subjects were exposed to SonoVue and comprise the pooled integrated safety database for the clinical program conducted in North America, Europe, and Asia as of September 30, 2011:

• Healthy Volunteers (PK and clin-pharm)	128 subjects
• Cardiac Patient Population	1769 patients
• Macrovascular Patient Population	555 patients
• Microvascular Patient Population	2785 patients
• Special Patient Populations	38 patients
	Total - 5275 subjects

Post-Marketing Surveillance Data as of September 30, 2011 from outside the United States (US) are also summarized.

As of July 28, 2010, 6 clinical trials remain ongoing (2 studies in the cardiac patient population and 4 studies in the microvascular patient population) with 1,448 patients having been dosed with SonoVue.

7.1.2 Categorization of Adverse Events

Adverse Events in Clinical Trials

Overall, the incidence of adverse events (AEs) in clinical trials has been 11% in subjects exposed to SonoVue. The majority of AEs (97%) were nonserious and rapidly self-resolving. The incidence of adverse reactions in clinical trials has been 5.7% in subjects exposed to SonoVue. The most frequently reported adverse reactions were headache (1.1%), injection site reaction (0.9%), and nausea (0.5%).

The incidence of serious AEs is also very low (21 cases, 0.4%) with only 3 cases (0.06%) in whom the relationship with SonoVue could not be completely ruled out. Of the 21 patients with serious adverse events, 10 deaths (0.1%) were reported,

AEs - 572 (10.8%) patients experienced 931 AEs
303 (5.7%) study-related - majority mild resolved without sequelae
9 Severe AEs
21 (0.4%) Serious AEs
11 Serious AEs in Cardiac Studies
15 (0.3%) Discontinued due to AEs
10 (0.1%) Deaths

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse Events

The most frequently reported adverse events (>0.5%) experienced by the 5275 subjects in All Completed Studies adverse events were headache (109 subjects, 2%), followed by nausea (47 subjects, 1%), chest pain (33 subjects, 0.6%), chest discomfort (30 subjects, 0.6%), and injection site pain (26 subjects, 0.5%). All other adverse events occurred at a frequency of <0.5%.

Within clinical trials 572 (11 %) patients experienced 931 adverse events. 303 (6%) were considered to be study-related. The majority of adverse events were mild and resolved without sequelae. Nine were severe and 21 (0.4%) were serious. Eleven of the serious adverse events occurred within cardiac studies. Discontinuation occurred due to adverse events within fifteen patients (0.3%) (
Table 17**).**

Table 17 : Adverse Events by System Organ Class Reported in >0.5% of the Subjects, All Completed Studies (Healthy Volunteers and Patients), SonoVue

System Organ Class / Preferred Term	No. (%) of Subjects (N=5275)	
	Total	Related[a]
No. (%) of Subjects with at least 1 AE	572 (10.8)	303 (5.7)
Gastrointestinal Disorders		
Nausea	47 (0.9)	29 (0.5)
General Disorders/Administration Site Conditions		
Chest discomfort	30 (0.6)	16 (0.3)
Chest pain	33 (0.6)	9 (0.2)
Injection site pain	26 (0.5)	20 (0.4)
Nervous System Disorders		
Headache	109 (2.1)	59 (1.1)

[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Adverse Events by Formulation

A summary of adverse events by formulation of SonoVue received is presented for All Completed Studies in **Table 18**. The preliminary formulations of SonoVue (Formulations 1, 2, and 3) were used only in Phase I and early Phase II/III trials. The relative percentage of adverse events was somewhat higher in these early studies than in the later clinical trials conducted with the final formulation of SonoVue. There were no other marked differences among the 4 formulations with respect to the type of incidence of adverse events.

Table 18 : Summary of Adverse Events by Formulation, All Completed Studies (Healthy Volunteers and Patients), SonoVue

	No.(%) of Subjects Dosed			
	Formulation 1 (N=20)	Formulation 2 (N=60)	Formulation 3 (N=76)	Final (Marketed) Formulation (N=5119)
Category	Total / Related[a]	Total / Related[a]	Total / Related[a]	Total / Related[a]
No. (%) of subjects with at least 1 AE	6 (30.0) / 6 (30.0)	16 (26.7) / 15 (25.0)	14 (18.4) / 13 (17.1)	536 (10.5) / 269 (5.3)
No. (%) of subjects with at least 1 serious AE	0 / 0	0 / 0	0 / 0	21 (0.4) / 3 (0.1)
No. (%) of subjects who discontinued due to AEs	0 / 0	0 / 0	1 (1.3) / 1 (1.3)	15 (0.3) / 6 (0.1)
No. (%) of deaths	0 / 0	0 / 0	0 / 0	7 (0.1)[d] / 0
No of AEs[b]	11 / 10	21 / 20	27/ 25	872 / 436
No. (%) of subjects with at least 1 non-serious AE by intensity:[c]	6 (30.0) / 6 (30.0)	16 (26.7) / 15 (25.0)	14 (18.4) / 13 (17.1)	519 (10.1) / 266 (5.2)
Mild AEs	6 (30.0) / 6 (30.0)	15 (25.0) / 14 (23.3)	13 (17.1) / 12 (15.8)	412 (8.0) / 228 (4.5)
Moderate AEs	0 / 0	1 (1.7) / 1 (1.7)	1 (1.3) / 1 (1.3)	98 (1.9) / 37 (0.7)
Severe AEs	0 / 0	0 / 0	0 / 0	9 (0.2) / 1 (<0.1)

[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] Multiple occurrences of the same adverse event in a subject are counted individually.
[c] If a subject experienced more than 1 non-serious adverse event, the subject was counted only once at the maximum intensity.
[d] One additional patient, who experienced 2 serious adverse events during the clinical trial, was reported to have died outside of the protocol-defined adverse event reporting window for Study BR1-071. One other death occurred in a patient who died of myocardial infarction before receiving SonoVue in Study BR1-020.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Seventy clinical studies are included in the integrated safety database. SonoVue was administered intravenously, either as a slow bolus injection and/or as a continuous infusion. Many studies employed crossover dosing, in which patients received multiple doses of SonoVue and/or control agents, usually on the same study day. The control agents included saline and Albunex®. (At the time some of these studies were conducted, Albunex was the only contrast agent approved for use with ultrasound imaging. At present, Albunex is no longer marketed.) All 70 studies were open-label or single-blind with respect to on site assessments of safety.

For the 5144 patients in the All Patient Studies who had exposure to SonoVue, the mean total volume administered was 10.25 mL (range: 0.3 to 161.3 mL).This includes patients who received multiple bolus doses of SonoVue in crossover studies as well as those who received infusion dosing. Seventy-three percent (73%) of the patients were in the group receiving cumulative doses ranging from greater than1.0 mL to 10 mL; 93%

receiving cumulative doses ranging from greater than 1.0 mL to 50 mL. Three additional subjects received SonoVue at an 'unknown' total volume. A 5 mg/mL concentration of SonoVue was used in all studies except study BR1-025, a Phase I dose escalation safety study in which a 15 mg/mL concentration was used.

For the 1766 patients in the Cardiac Population Studies with exposure to SonoVue, the mean total volume administered was 16.39 mL (range: 0.5 to 161.3 mL). This includes patients who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. Sixty-three percent (63%) of the patients received cumulative doses ranging from greater than 1.0 mL to 10 mL; 91% received cumulative doses ranging from greater than 1.0 mL to 50 mL.

In the three Phase III Studies ((BR1-19A, BR1-19B and BR1-013) 191 patients received the 2 mL proposed marketing dose as well as both lower and greater doses. In fact, the majority of these patients, 137 also received 0.5, 1.0 and 4.0 mL doses, for a total of four doses.

7.2.2 Explorations for Dose Response

Based on the results from all studies (demonstrated in most Tables in this document), the useful contrast effect and endocardial delineation scores increased as doses of SonoVue increased from the 0.05 mL through the 2.0 mL dose. However, the 4.0 mL highest dose evaluated did not demonstrate any advantage over the 2.0 mL dose. Therefore, we agree that the data support the selection of the 2 mL dose as .the proposed marketing dose.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing is required.

7.2.4 Routine Clinical Testing

Patients need to be screened for known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts. SonoVue administration is contraindicated in patients with these shunts due to the risk of cerebral injury.

7.2.5 Metabolic, Clearance, and Interaction Workup

SF_6 does not undergo biotransformation. The SF_6 contained in SonoVue is eliminated via the lungs. Twenty minutes following injection, the mean cumulative recovery of SF_6 in expired air was 82 ± 20% (SD) at the 0.03 mL/kg dose and 88 ± 26% (SD) at the 0.3 mL/kg dose.

SF_6 undergoes a substantial degree of first pass elimination within the pulmonary circulation; approximately 40-50% of the SF_6 content was eliminated in the expired air during the first minute following SonoVue injection. At 11 minutes post dose, approximately 80-90% of the SF_6 content was eliminated.

Palmitic acid and the phospholipids, distearoylphosphatidylcholine and dipalmitoylphosphatidylglycerol sodium, present in trace quantities in SonoVue to form a monolayer around the gas bubble, are metabolized via normal metabolic routes in the body.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Two additional microsphere products are available with similar indications for delineation of left ventricular border and to opacify the left ventricle with suboptimal echocardiograms. Both Definity and Optison, intravenously administered microsphere contrast imaging agents, have been associated with infrequent immediate onset serious life-threatening anaphylactoid events. Therefore, they all carry a similar Black Box Warning within their label.

7.3 Major Safety Results

The major safety concern associated with the administration gaseous ultrasound microsphere contrast agents intravenously, including SonoVue, is the uncommon and unpredictable occurrence of the onset of serious life-threatening events that can occur either during or immediately following administration. These reactions involve the immune, cardiac, vascular, respiratory, and nervous systems and are thought to be anaphylactoid –related. Whereas this class of imaging agents has the potential to be associated with serious adverse anaphylaxis and death, microsphere contrast agents all carry a similar Black Box Warning within their label.

7.3.1 Deaths

Fatalities within Clinical Studies

A total of 10 deaths were reported in all the clinical studies conducted with SonoVue from 1993 to date. All of these deaths were considered to be unrelated to the administration of SonoVue.

Within 70 clinical trials, 6723 subjects have been dosed with SonoVue. 5275 subjects were exposed to SonoVue in completed studies and 1448 patients have been dosed within ongoing studies. From among the 5,275 subjects who received SonoVue in clinical trials, ten (10) deaths were recorded from 1993 to date. All deaths were considered to be unrelated to administration of SonoVue by both the investigators and Bracco.

The 10 deaths within clinical studies can be considered unrelated to the administration of SonoVue and are summarized here:

1 patient died before receiving SonoVue
2 patients had procedural complications during percutaneous coronary interventions following a well-tolerated SonoVue ECHO exam
1 patient died after undergoing right hepatectomy
6 patients died 10 to 26 days after exposure to SonoVue. In none of these six cases did the death follow any reaction or complication related to the administration of SonoVue

Fatalities during Post Marketing Surveillance

Among the estimated (b) (4) patients exposed to SonoVue during the market use of the product, deaths were reported for nine (9) patients (during the period 2001-Sept 30, 2011). Three deaths occurred before 2005, six in 2005 or later. Narrative summaries for each case were provided. **Table 19** summarizes the medical narratives, onset of fatal adverse events and reviewer's assessment of likely causality.
Nine fatalities have been reported within the postmarketing surveillance since the launch of the product. Three deaths were considered to be probably related, four deaths were considered to be possibly related to the administration of SonoVue and two deaths were considered to be unrelated to the administration of SonoVue.

Table 19 : Summary of Fatal Outcomes Reported in Postmarketing Surveillance

Case ID/ Country	Medical Narratives – Fatal Outcomes	AE Onset Post CUS			Causality
		Sec	Min	Hours	
DE-000545* Germany	Patient developed anaphylactic reaction/ shock and acute myocardial infarction post CUS. Died 40 min post CUS.	30			Probable
DE-000635* Germany	Patient developed anaphylactoid reaction post CUS for unknown indication. Died same day.		1		Probable
BRO-011933* Norway	Patient developed dyspnea, cough & strange taste, unconsciousness, seizure post CUS for liver metastases. Failed resuscitation. Died 40 min post CUS.	15			Probable

NL-000008* Netherlands	Patient developed anaphylactic reaction & sudden death post CUS while a myocardial infarction was evolving. Died 40 min post CUS.		2		**Possible**
BRO-005943* Germany	Patient with myocardial infarction developed bradycardia, hypotension, loss of consciousness & ventricular fibrillation post second CUS for stent occlusion. Died same day.		4-5		**Possible**
BRO-006772 Germany	Patient with myocardial infarction post angioplasty developed loss of consciousness & asystole post CUS. Died 40 min post CUS.		?		**Possible**
CN-000162* China	Patient developed cough & nausea, shock & coma post liver CUS for anorexia.	40-60	<1		**Possible**
BCM-000767 Italy	Patient following PTCA developed irreversible cardiac arrest post CUS. Autopsy finding complete thrombosis common coronary trunk		2		**Unrelated**
BRO-008552 Sweden	Patient developed loss consciousness, dyspnea & abdominal pain few min post morphine injection post liver CUS			9	**Unrelated**

7.3.2 Nonfatal Serious Adverse Events

As of the clinical cut-off date of this document (September 30, 2011), 13 patients in 5 Ongoing Bracco-Sponsored Clinical Studies reported serious adverse events. A description of each case is provided below.

- Case 011949 (Study BRA/013, Patient No. 01/07, SonoVue dose: 2 mL), a 65-year-old male patient with CAD and arterial hypertension who underwent a 3D echocardiography to assess LV function. About 1 to 2 minutes after the intravenous injection of 2 mL of SonoVue during a rest examination, the patient experienced anaphylactic shock which consisted of heat sensation, asystole, loss of consciousness and hypotension. The patient was treated with atropine, adrenaline, corticosteroids, fluids, dimetindene maleate, and ranitidine. The patient was hospitalized in the intensive care unit (ICU) for further observation. The outcome was reported as recovered within 30 minutes. The patient had no history of allergy. The patient had never received SonoVue before, but was exposed to another contrast agent (Iodixanol) 2 weeks prior to this examination

without experiencing any adverse reaction. The reporter considered the adverse events to be related to the investigational product.

- Case IT-000256 (Study BR1-125, Patient No. 1602, SonoVue dose: 0.7 mL), a 73-year-old male patient with respiratory COPD, angina of effort and hypertension who underwent a stress echocardiography for known or suspected CAD. After an infusion of an unknown amount of dipyridamole and at the peak of the stress, the patient received 0.7 mL of SonoVue and experienced hypertension for which he was administered 0.6 mg of nitroglycerin spray. No ECG changes were noted at the onset of the adverse event. The patient was hospitalized and the reaction resolved on the same day. The patient had a known history of hypertension for which he had been taking valsartan 80 mg since 1998. The patient had not taken his antihypertensive medication on the day of the examination. The patient was discontinued from the study due to the adverse event. The Investigator assessed the event as not related to SonoVue administration.

- Case DE-000297 (Study BR1-125, Patient No. 1101, SonoVue 9 mL), a 69-year-old female patient with systolic hypertension, suspected myocarditis (in 2005) and allergy to sulfonamide (occurred more than 20 years ago), who underwent a pharmacological stress test to rule out suspected coronary artery disease. The patient received 6 mL SonoVue and underwent echocardiography. Once the procedure was completed, 50 mg of dipyridamole was infused in 4 minutes time, immediately followed by 3 mL of SonoVue for the stress portion of the echocardiography. The patient was reported to have increased heart rate followed by extra systole, bradycardia, and short term asystole (duration of 30 seconds). The reaction resolved approximately 1 hour after the patient was treated with atropine, methylprednisolone, ranitidine hydrochloride, dimetindene maleate, and hydroxylethyl starch solution. The patient was discontinued from the study due to the adverse event. The Investigator assessed the event as probably related to the administration of the investigational product.

- Case FR-000274 (Study BR1-125, Patient No. 3317, SonoVue unknown mL), a 83-year-old male patient with a history of abdominal aorta aneurysm (treated with stent implantation in 2008), arrhythmia (treated with flecainide), hypertension, dyslipidaemia, overweight and recently found to suffer from chronic occlusion of the circumflex artery with a known right coronary stenosis (more than 50% occluded), underwent an echocardiography with an unknown dose of SonoVue on (b) (6) On (b) (6), a non-sustained ventricular tachycardia was noted on the reading from a systematic Holter ECG which was placed on the patient immediately after the enhanced myocardial echocardiography was performed the day before. The reaction resolved on (b) (6) following hospitalization and treatment with amiodarone and bisoprolol (5 mg/day). The

Investigator assessed the event as unrelated to the administration of SonoVue, but rather a result of the patient's underlying disease.

- Case FR-000317 (Study BR1-125, Patient No. 3321, SonoVue 9.2 mL), an 80-year-old female patient with a history of coronary angiography and diabetes, was enrolled in a clinical trial to compare SonoVue-enhanced myocardial echocardiography to ECG-gated single photon emission computed tomography (SPECT), at rest and at peak of low-dose dipyridamole stress test, in the assessment of significant CAD. A coronary angiography performed on (b) (6) showed bi-troncular coronary disease (i.e., calcified ostium of left descending artery and sub-occluded left marginal branch). Due to the patient's age and diabetes, the physician decided to perform coronary left descending artery angioplasty. On (b) (6) SPECT was performed with no problem. Two days later, stress echocardiography was performed with 4.3 mL of SonoVue, followed by 30 mg of dipyridamole and then another 4.9 mL of SonoVue. No pain was reported by the patient; no ECG modifications, no hemodynamic variability and no rhythm alterations were noted. Two hours after the completion of the stress echocardiography, angioplasty, defined as complex (severe and calcified ostial proximal left descending artery) with the use of rotablator and successive balloon inflations, was performed. The patient experienced acute coronary rupture during balloon inflation (left main distal) complicated by massive hemopericardium. Emergency pericardial drainage was performed, but the patient had hemodynamic cardiac shock and died 35 minutes later, despite intensive reanimation. The investigator considered the events to be unrelated to the administration of SonoVue, but rather a result of acute ballooning of the left main artery.

- Case IT-000765 (Study BR1-127, Patient No. 1007, SonoVue 0.6 mL), a 64-year-old male patient with unknown medical history, underwent a guided prostate biopsy after administration of 0.6 mL of SonoVue i.v. (duration of the administration: 10 minutes). About 6 hours after SonoVue administration, the patient experienced acute urinary retention. A bladder catheter was positioned to treat the urinary retention, which resolved in about 30 minutes. The investigator considered the event as unrelated to SonoVue.

- Case US-006006 (Study BR1-128, Patient No. 0204, SonoVue 2.4 mL), a 75-year-old female with stage 4 chronic renal insufficiency, hypertension, hyperlipidemia, secondary hyperparathyroidism and gout underwent a contrast-enhanced hepatic ultrasound with 2.4 mL of SonoVue. Five days later, the patient underwent an elective in-hospital laparoscopic cholecystectomy and developed metabolic acidosis which prolonged her hospital stay for an additional day. The patient was treated and recovered the next day. The Investigator considered the metabolic acidosis to be a result of her underlying disease and, therefore, unrelated to the administration of SonoVue.

- Case US-004158 (Study BR1-128, Patient No. 0403, SonoVue 2.4 mL), a 54-year-old male who had a liver lesion for which he was undergoing a liver transplant work-up. The patient received 2.4 mL of SonoVue and the hepatic ultrasound was completed without incident. Five days later, he was found by the liver transplant team to be dehydrated and with orthostatic hypotension upon admission for further work-up of his liver lesion. The patient recovered 2 days later. The Investigator assessed the event as unrelated to the administration of SonoVue, but rather a result of the patient's underlying disease.

- Case US-006491 (Study BR1-128, Patient No. 0452, SonoVue 2.4 mL), a 54-year-old female with a history of possible allergy to iodine and long-term intermittent right upper quadrant pain underwent a contrast-enhanced hepatic ultrasound with 2.4 mL of SonoVue. Over 24 hours later, she underwent an ultrasound-guided core liver biopsy without contrast, according to the study protocol. The biopsy was uneventful. Fifteen to 20 minutes after the biopsy, the patient experienced a moderate degree of right upper quadrant pain, and her blood pressure dropped to approximately 53/35 mmHg, but her heart remained stable (values not provided). The patient was placed in a reverse Trendelenburg position and received increased intravenous fluids. Her blood pressure rapidly returned to normal. The Investigator considered the drop in blood pressure to be related to the biopsy, therefore not due to the administration of SonoVue.

- Case US-004554 (Study BR1-128, Patient No. 0602, SonoVue 2.4 mL), a 71-year-old male with a history of deep venous thrombosis (DVT) who underwent a hepatic ultrasound and on the evening experienced abdominal pain, right shoulder pain, and worsening in shortness of breath. A computed tomography (CT), performed the next day, revealed a bilateral upper lobe pulmonary embolism. The patient was treated with sodium chloride 0.9% i.v. bolus 500 mL, acetylcysteine 20% Oral Solution 600 mg, heparin i.v. bolus 7000 units, heparin i.v. continuous infusion 1500 units/hr, and oxycodone enteral 10 mg oral. He recovered without sequelae and was discharged home 6 days after the ultrasound procedure. The Investigator considered the event to be unrelated to the administration of SonoVue, but rather were due to the patient's underlying conditions with DVT.

- Case US-005915 (Study BR1-128, Patient No. 0722, SonoVue 2.4 mL), a 49-year -old male with a medical history of liver mass, hepatitis C virus and alcoholic cirrhosis underwent a contrast-enhanced hepatic ultrasound with 2.4 mL of SonoVue on (b) (6) He tolerated the procedure well and appeared well at his 24-hour follow-up visit. On (b) (6) a CT-guided biopsy and fiducial seed placement for a liver mass were performed, according to the study protocol. He was discharged home following the procedure. The next day he developed shortness of breath, chest pain, and dizziness. Evaluation at an

outside hospital revealed a hematocrit of 24, down from a hematocrit in the 40's in December of 2010. The patient was transfused with 2 units of blood and imaging revealed a large right hemothorax requiring admission to the ICU. He was treated and recovered (with sequelae). The Investigator considered the massive hemothorax was a result of the CT-guided biopsy and fiducial placement procedure performed 24 hours after the administration of SonoVue and, therefore, not related to the administration of SonoVue.

- Case US-005871 (Study BR1-130, Patient No. 0404, SonoVue 2.4 mL), a 61-year-old female with a history of stage III breast cancer (diagnosed and treated in 1996) who developed metastatic lesions in the bone, lung and liver underwent a contrast-enhanced hepatic ultrasound on (b) (6) The hepatic ultrasound was completed with no reported complications. Two days later, she began chemotherapy for metastatic breast cancer. Four days after starting chemotherapy, the patient became dehydrated and was admitted to the hospital the next day where she was treated with intravenous fluids. The patient's overall condition was deteriorating and she became less responsive. She remained hospitalized for 17 days before being discharged home with care by the hospice team and her very supportive family. The patient died on (b) (6) of metastatic breast cancer. An autopsy was not performed. The Investigator considered the dehydration to be a result of the chemotherapy on top of the general debility from metastatic breast cancer, and unrelated to the administration of SonoVue.

- Case US-006381 (Study BR1-130, Patient No. 0422, SonoVue 4.8 mL), a 76-year-old male with stage 3 colorectal cancer, diabetes, hypertension, Wegner's granulomatosis, chronic renal insufficiency, demyelinating peripheral neuropathy, superficial spreading melanoma, left arm paralysis secondary to an accident 20 years ago, left total hip replacement and obstructive sleep apnea underwent a contrast-enhanced hepatic ultrasound with 4.8 mL of SonoVue. Six days later, the patient was hospitalized with progression of metastatic colon cancer after weeks of increasing weakness, fatigue and abdominal pain. He was treated with intravenous fluids, unspecified analgesics and 2 units of packed red blood cells. Two days later, the patient was in acute distress; he had a "Do Not Resuscitate" order, was therefore not resuscitated and expired the same day. The Investigator considered the progression of metastatic colon cancer to be related to the patient's underlying disease, therefore not related to the administration of SonoVue.

One additional serious adverse event was reported outside of the protocol-defined adverse event reporting window (from the time of signed Informed Consent through 24 hours post-dose) for Study BR1-127. Case FR-000298 (Study BR1-127, Patient No. 0610) was a 71-year-old male patient who received a total volume of 4.8 mL of SonoVue while undergoing a contrast enhanced ultrasound examination of the prostate.

On the same day, the patient also underwent a systematic biopsy. He completed the study on the subsequent day with onset of prostatitis, which was considered to be mild in intensity, and unrelated to the administration of SonoVue. The patient was hospitalized the following day (1 day after study completion) with a worsening of symptoms, including fever and chills. The Investigator considered this event to be unrelated to the administration of SonoVue.

7.3.3 Dropouts and/or Discontinuations

Of the 5275 subjects who received SonoVue, 5002 (94.8%) completed the studies, while 273 (5.2%) discontinued prematurely (17 for adverse events, 4 for lost to follow-up, 37 for withdrawal of consent, 2 for protocol violations, 211 for other reasons [such as no treatment (including no surgery or no radio frequency ablation)], and 3 for no reason specified).

16 (0.3%) of the 5275 subjects administered with SonoVue discontinued due to adverse events in the All Completed Studies. Of these 16 subjects, 9 subjects reported events that were considered unrelated to SonoVue administration. The most commonly reported study agent-related adverse events resulting in discontinuation were nausea and hypotension, each reported by 2 subjects each (<0.1%). All other study agent related adverse events resulting in discontinuation occurred in 1 subject each. Of the 5147 patients who received SonoVue, 4877 (94.8%) completed the studies, while 270 (5.2%) discontinued prematurely (16 for adverse events, 4 for lost to follow-up, 37 for withdrawal of consent, 2 for protocol violations, 209 for other reasons, and 3 for no reason specified).

A total of 1781 patients participated in the Completed Cardiac Studies. In these studies, 12 patients discontinued prior to receiving SonoVue. Of the 1769 patients who received SonoVue, 1694 (95.8%) completed the studies, while 75 (4%) discontinued prematurely (11 for adverse events, 1 for lost to follow-up, 3 for withdrawal of consent, and 60 for other reasons).

A summary of adverse events resulting in discontinuation in the Completed Cardiac Studies is provided in **Table 20**.

Table 20 :Summary of Adverse Events Resulting in Discontinuation in Completed Cardiac Studies

Study No.	Pt. No.	Adverse Event MedDRA Term	Relationship to Study Agent	Death	SAE	DC'd
BR1-020	0141	Fatigue	Not related			X
BR1-021	0015	Bradycardia	Possible			X
		Hypotension	Possible			X
BR1-041	0014	Cardiogenic shock	Not related	X	X	X
BR1-041	0063	Ventricular rupture	Not related		X	X
BR1-066	0101	Angina Unstable	Not related			X
BR1-066	0402	Anxiety	Not related			X
BR1-066	0604	Angina Pectoris	Not related			X
		Ventricular tachycardia	Not related			X
BR1-066	1403	Chest pain	Unknown*		X	X
		Electrocardiogram ST segment elevation	Unknown*		X	X
		Hypotension	Unknown*		X	X
* Relationship 'unknown' in clinical trial database, however, subsequent information received from the Investigator indicated that the events were clearly related to ischemia triggered by dobutamine.						
BR1-066	1501	Hot Flush	Possible			X
		Nausea	Possible			X
BR1-112	1018	Swollen tongue	Probable			X
BBG-001	0403	Headache	Not related			X
BBG-001	1504	Rash	Probable		X	X
		Presyncope	Probable*		X	X
* Relationship 'probable' in clinical trial database, however, subsequent information received from the Investigator indicated that the vasovagal event was not directly related to SonoVue administration. Data source: *Integrated Summary of Safety Patient Data Listing 1.3.*						

7.3.4 Significant Adverse Events

The majority of serious event cases reported with SonoVue were immune system disorders (146 cases), with the second most frequently reported serious events being cardiac system disorders (64 cases).

Immune System Disorders

Of the 246 patients reporting serious reactions, 146 (59%) were diagnosed by the initial reporter as allergy-like (e.g., anaphylactic/anaphylactoid reaction, anaphylactic shock, hypersensitivity) reactions (**Table 21**). According to a systematic review of the serious ADR reports performed by Bracco, an additional 39 ADR cases should be medically classified as allergy-like events. Therefore, a total of 185 out of 246 patients with serious ADR had an allergy-like reaction and the overall incidence of serious allergic reactions is estimated to be in the order of 1:10,000 exposed to SonoVue as of

September 30, 2011. In most cases allergy-like events presented an onset within a few minutes from the injection of the product. In 39 of the 185 serious allergy-like reactions, hypotension (preferred terms: hypotension, blood pressure decrease, blood pressure immeasurable, syncope, presyncope, circulatory collapse, and pulse pressure decrease) was reported at the onset of the allergy-like reaction. The severity of hypotension could range from a reduction of a few millimetres of mercury in SBP and DBP to non-measurable levels.

Table 21 : Post-marketing Spontaneously Reported Immune Adverse Reactions – Total Estimated Exposure to SonoVue: (b) (4) Patients as of 30 September 2011

MedDRA System Organ Class Preferred Term ---------- Immune System Disorders	Number (%) of Events					
	Serious		Non-Serious		Total	
	Count	RR% in Exposed Patients	Count	RR% in Exposed Patients	Count	RR% in Exposed Patients
Anaphylactic reaction	35	(b) (4)	0	(b) (4)	35	(b) (4)
Anaphylactic shock	56		0		56	
Anaphylactoid reaction	21		4		25	
Anaphylactoid shock	2		0		2	
Contrast media allergy	1		0		1	
Drug hypersensitivity	1		1		2	
Hypersensitivity	31		14		45	
Sub-Total						
Adverse events	147		19		166	
Patients with AEs	146		19		165	

Cardiac System Disorders

One of the issues considered with respect to the post-marketing surveillance database are the cardiac events. A total of 73 patients experienced 85 cardiac-relate adverse drug reactions during the post-marketing surveillance period of April 1, 2001 to September 30, 2011. Of the 73 patients, 64 ((b) (4) of exposed patients) experienced serious cardiac-related adverse reactions (**Table 22**). In the remaining serious cases, an additional 29 cases (preferred terms: blood pressure decreased, blood pressure immeasurable, electrocardiogram ST segment elevation, heart rate decreased, pulse abnormal pulse absent, pulse pressure decreased, hypotension, shock, and circulatory collapse) were included in the count of serious cardiac-related cases for a total of 93

patients. Less than half of these cases (42 out of 93; 45.2%) were associated with allergy-like/anaphylactoid reactions.

Table 22 : Post-marketing Spontaneously Reported Cardiac Adverse Reactions – Total Estimated Exposure to SonoVue: (b) (4) Patients as of 30 September 2011

MedDRA System Organ Class Preferred Term ---------- Cardiac Disorders	Number (%) of Events					
	Serious		Non-Serious		Total	
	Count	RR% in Exposed Patients	Count	RR% in Exposed Patients	Count	RR% in Exposed Patients
Acute myocardial infarction	2	(b) (4)	0	(b) (4)	2	(b) (4)
Angina pectoris	2		0		2	
Arrhythmia	1		0		1	
Arteriospasm coronary	2		0		2	
AV block complete	2		0		2	
AV block first degree	1		0		1	
AV block second degree	0		1		1	
Bradycardia	19		1		20	
Bundle branch block left	1		1		2	
Cardiac arrest	13		0		13	
Cardiac failure	1		0		1	
Cardio-respiratory arrest	2		0		2	
Cardio-respiratory distress	1		0		1	
Cardiovascular disorder	1		0		1	
Cyanosis	3		1		4	
Myocardial infarction	3		0		3	
Myocardial ischemia	1		0		1	
Palpitations	0		1		1	
Prinzmetal angina	2		0		2	
Sinus tachycardia	1		0		1	
Tachycardia	12		2		14	
Torsade de pointes	1		0		1	
Ventricular fibrillation	2		0		2	
Ventricular hypokinesia	1		0		1	
Ventricular tachycardia	2		2		4	
Sub-Total						
Adverse events	76		9		85	
Patients with AEs	64		9		73	

7.3.5 Submission Specific Primary Safety Concerns

Clinical pharmacology and safety studies have been conducted to detect any specific effect of SonoVue on:

- oxygen saturation, vital signs and ventricular repolarization in patients with coronary artery disease by 12-lead continuous ECG monitoring (one study with insonation at low and high mechanical index [MI]);
- pulmonary hemodynamics in patients with congestive heart failure and pulmonary hypertension;
- oxygen saturation, vital signs, and pulmonary function in patients with moderate to severe chronic obstructive pulmonary disease;
- pharmacokinetics, oxygen saturation, vital signs, and ECG in patients with diffuse interstitial pulmonary fibrosis.

None of these studies showed any significant effect on pulmonary hemodynamics, pulmonary function, blood pressure, oxygen saturation, vital signs, cardiac function, electrocardiographic parameters and laboratory test results.

Supportive Safety Results

Data from the following 2 clinical trials that were completed (have a final clinical trial report) at the time of this New Drug Application (NDA) submission, but were not integrated into the pooled safety database are presented individually:

- Study BR1-133 was a Phase II, double-blind, randomized, placebo-controlled, crossover safety study of the effect of intravenous bolus injections of SonoVue on pulmonary hemodynamics in patients with and without pulmonary hypertension.

- Study BR1-129 was a Phase II explorative multicenter study with intra-patient comparison of SonoVue-enhanced ultrasonography in subjects with advanced HCC.

These 2 studies will be integrated into the pooled safety database for the first safety update following this submission.

Five other studies were ongoing (final clinical trial report not yet available) as of September 30, 2011. Any studies which are considered to be completed as of the data cut-off date for the first safety update following this submission may be integrated into the pooled safety database.

Two clinical studies were conducted in Japan. The studies are not included in the Integrated Safety Database. No deaths or serious adverse events were reported in either study.

In Study E7210-J081-001, 26 adverse events were observed in 17 of 42 subjects (40.5%); 17 adverse events were observed in 10 of 28 SonoVue-dosed subjects (35.7%), and 9 adverse events were observed in 7 of 14 placebo-dosed subjects (50.0%). Of the 26 adverse events, 12 were reported from physical examinations, and 14 were reported from laboratory investigations. In Study E7210-J081-002, 3 adverse events were reported for 3 of the 12 subjects dosed with SonoVue (trauma [fall from bicycle], decreased DBP and increased SGOT).

7.4.1 Common Adverse Events

The adverse events experienced most frequently (>0.5%) in All Patient Studies were headache (102 patients, 2.0%), nausea (46 patients, 0.9%), chest pain (33 patients, 0.6%), chest discomfort (29 patients, 0.6%), and injection site pain (24 patients, 0.5%). All other adverse events occurred at a frequency of <0.5%.

Among the Completed Cardiac Studies the most commonly reported adverse events (>0.5%) were headache (75 patients, 4.2%); chest pain and nausea (31 patients each, 1.8%); chest discomfort (26 patients, 1.5%); dyspnea (13 patients, 0.7%); angina pectoris, blood glucose increased, dysgeusia (11 patients each, 0.6%); pain in extremity and dizziness (10 patients each, 0.6%); hypotension (9 patients, 0.5%); and abdominal pain upper, fatigue, feeling hot, and tremor (8 patients each, 0.5%).

The most commonly reported study agent-related adverse events (>0.5%) were headache (35 patients, 2.0%), nausea (19 patients, 1.1%), chest discomfort (13 patients, 0.7%), dysgeusia (11 patients, 0.6%), and chest pain and blood glucose increase (8 patients each, 0.5%).

7.4.2 Laboratory Findings

A small number of patients had increases and decreases in hematology, serum chemistry, and urinalysis values that met the criteria for substantial changes from baseline. The incidence of specific marked abnormalities was low and reported in $\leq$3.4%, $\leq$2.9% and $\leq$1.2%, respectively, of the subjects.

A similar trend was observed in the Completed Cardiac to that observed in the All Patients studies. There were no clinically meaningful trends in hematology, serum chemistry, or urinalysis parameters. Individual values which met the sponsor's criteria for marked abnormality were infrequent.

7.4.3 Vital Signs

The number of subjects reporting vital sign values with changes from baseline outside the normal reference range was small and comparable between SonoVue and placebo for both hemodynamic groups. Only 1 subject in the Hypertension Group experienced a change in DBP that was considered of potential clinical importance (decrease from baseline of ≥10 mmHg).

Less than 40% of subjects in the SonoVue group and <33% of subjects in the placebo group had O_2 Sat values below the normal reference range while <33% of subjects amongst the 2 investigational product groups had values above the normal reference range. No subject had values meeting the criteria for potential clinical importance. No subject presented with clinically significant changes in laboratory tests at 24 hours from the administration of the test compound.

7.4.4 Electrocardiograms (ECGs)

For quantitative ECG parameters, the number of subjects with changes from baseline of potential clinical importance was small, with no significant differences between SonoVue and placebo for both hemodynamic groups. The qualitative assessment of ECG after administration of SonoVue did not show any change at any time-point, among subjects in the hypertension or the normal group. In addition, no subjects had a clinically significant worsening from baseline in either qualitative or quantitative ECG parameters over the 24-hour follow-up.

In the continuous ECG studies, there were no statistically significant differences in the maximum increases from baseline in corrected QT interval following administrations of SonoVue and a placebo (physiologic saline), no evidence of a dose-response relationship or relationship to different mechanical index of ultrasound applied during echocardiography.

During stress, there were about the same increases and decreases in heart rate at 0 minute and more increases than decreases at 5 minutes and only increases with no decreases at 9 minutes, as can be expected during stress. The majority of increases in heart rate was 30 bpm or less, except that 11.5% of the patients at 5 minutes and 10.0% of the patients at 9 minutes had heart rate increases >30 bpm. No decreases greater than 20 bpm were recorded at any of these time points.

After the last SonoVue injection at peak stress, there were more increases than decreases both in number of patients and in magnitude in all time points including 5 minute, 10 minutes, 30 minutes, 1 hour and 24 hours. All the increases in heart rate were <30 bpm and all the decreases were <20 bpm. At 30 minutes and 1 hour post dose, all increases in heart rate were <20 bpm. No specific effect of SonoVue on heart rate was detected during stress.

Clinically significant changes from baseline in QT interval for patients who had values at baseline and at 0 minute, 5 minutes, and 9 minutes during stress testing and at 5 minutes, 10 minutes, 30 minutes, 1 hour and 24 hours after last SonoVue injection were evaluated. During stress, there were similar increases and decreases at 0 minute in QT interval. As expected, as the heart rate increases due to the stress effect, there were fewer increases and more decreases in QT interval. There were no increases in QT >60 msec at any time point and only 1 patient each had increases between 21-30 and 31-60 msec at 0 and 9 minutes during stress.

At 5 minutes after the last SonoVue injection during stress, 88% of patients experienced decreases in QT interval (61% ≤30 msec, 25% between 31-60 msec and 2% >60 msec) compared to only 12% of patients with QT interval increases of 20 msec or less. This phenomenon became less and less pronounced at the following time points as the stress effect was wearing off. There were no increases in QT >60 msec at any time point and only 1 patient each had decreases >60 msec at 5 minutes and 24 hours post dose.

During stress, the majority of changes in both QTc Bazett and QTc Fridericia were within 30 msec. There were slightly more increases than decreases in QTc Bazett at 5 and 9 minutes and similar increases and decreases across all time points in QTc Fridericia. Increases or decreases of QTc >60 msec occurred rarely at sporadic time points.

After the last SonoVue injection (during stress), the majority of changes in both QTc Bazett and QTc Fridericia were within 30 msec, few were >30 msec. There were slightly more increases than decreases in QTc Bazett across all time points, except at 24 hours when there were more decreases than increases. The increases and decreases in QTc Fridericia were similar in frequency and magnitude across all time points, except at 24 hours when there were more decreases than increases, representing a pattern of normal variation. Increases or decreases of QTc >60 msec occurred very rarely at sporadic time points after the last SonoVue injection. For QTc Bazett, increases were observed at 10 minutes and 24 hours and decreases at 5 minutes post dose. For QTc Fridericia no increases were observed at any time point and decreases only at 5 minutes.

In conclusion, the effect of SonoVue on ventricular repolarization and, in general on cardiac electrophysiology was superimposable on that for placebo. There was no evidence of a dose- response relationship in the incidence of changes of potential clinical importance for ECG parameters.

The results of the continuous ECG studies support the following conclusions:

- Administration of SonoVue at doses 0.1 or 0.5 mL/kg does not appear to cause prolonged cardiac repolarization in patients with CAD undergoing B-

mode echocardiography with a wide range of clinically relevant MI settings - from low (0.4-0.5) to high (1.5-1.6).

- There is no statistically significant difference between SonoVue and placebo in the maximum increase from baseline in corrected QT interval following administration of study agent and no evidence of a dose-response relationship.
- Administration of SonoVue is not associated with any increased incidence of cardiac abnormalities as evaluated by quantitative and qualitative ECG parameters.

7.4.5 Special Safety Studies/Clinical Trials

- **Study 133**
  Bracco performed a pulmonary hemodynamic safety study as recommended by the FDA to assess safety among patients with pulmonary hypertension. 36 patients scheduled for right heart catheterization [18 MPAP $\geq$25 mmHg & 18 HV <25 mmHg] participated in an intra-patient cross-over study. Vital sign values with changes from baseline outside the normal reference range were small and comparable between SonoVue and placebo for both hemodynamic groups.

  Only 1 subject in the Hypertension Group experienced a change in DBP that was considered of potential clinical importance (decrease from baseline of ≥10 mmHg). No subject had O_2 Sat values meeting the criteria for potential of clinical importance.

- **Study 129**

  Bracco performed a Phase II explorative multicenter study with intra-patient comparison of SonoVue-enhanced ultrasonography in subjects with advanced HCC. One non-serious adverse event of SBP increase was reported for Subject No. 801, 29 minutes after receiving one administration of 2.4 mL of SonoVue at Week 4 (Visit 3). The event was considered by the Investigator to be mild in intensity and of unknown relationship to the administration of the investigational product. The subject recovered after 1 hour. No other adverse events were reported.

  Changes from each visit's pre-dose value of potential clinical importance among the vital sign parameters were noted for 2 subjects. Subject No. 106 had a pre-dose SBP of 140 mmHg which increased 25 mmHg at 5 and 30 minutes after the first injection at Week 24 (Visit 6). The subject did not receive a second bolus and, due to the termination of the study, did not return for a follow-up visit; however, no adverse event was reported for this subject. Subject No. 402 had a pre-dose heart rate value of 115 bpm which was outside of the normal reference range and had decreased 10 bpm at 5 and 30 minutes after the first injection of

SonoVue; his heart rate was within the normal reference range at both time points after the second injection (100 bpm).

7.4.6 Immunogenicity

A total of 185 cases after SonoVue administration were allergy-like or anaphylactoid in nature (0.0096%). In about half of the hypersensitivity cases, symptoms in other system organ classes (SOCs) were also reported, among which events of cardiac, vascular, respiratory, neurology and skin/subcutaneous tissue were the most frequently reported, consistent with the typical signs and symptoms of serious hypersensitivity reactions with multi-organ system involvement.

In general, the observed pattern of serious hypersensitivity reactions is similar to that reported for anaphylactic or anaphylactoid reactions to other ultrasound contrast agents or intravascular imaging agents. In most of these cases of apparent hypersensitivity, the initial signs or symptoms started within 5 minutes from the injection of SonoVue. The initial symptoms ranged from mild to severe and could progress to medically important or life-threatening events.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In all clinical trials with SonoVue, a total of 5275 adult subjects (128 healthy volunteers and 5147 patients) received SonoVue at cumulative doses ranging from 0.2 to 161 mL (mean 10.3 mL). This includes subjects who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. The majority (77%) of subjects received SonoVue at cumulative doses of 10 mL or less.

The most commonly reported adverse reactions in adult subjects who received SonoVue were headache (1.1%) and nausea (0.5%). In addition, local injection site reaction (including application site paraesthesia, injection site coldness or warmth, erythema, swelling, and pain) occurred in 0.9% of all subjects. Most adverse reactions were mild to moderate in intensity and resolved spontaneously.

7.5.2 Time Dependency for Adverse Events

The onset of most adverse events occurred either during or within 30 minutes post intravenous-administration.

7.5.3 Drug-Demographic Interactions

There were 3263 (62%) men and 2011 (38%) women (1 patient, gender not reported) with a mean age of 58.3 years (range 17 to 99 years). A total of 4058 (76.9%) subjects

were Caucasian, 159 (3.0%) Black, 1000 (19.0%) Asian, 33 (0.6%) Hispanic, 22 (0.4%) in other racial groups, and for 3 (0.1%) subjects, race was not reported. No drug-demographic-related interactions were observed.

7.5.4 Drug-Disease Interactions

The risk for serious cardiopulmonary events may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias).

7.5.5 Drug-Drug Interactions

No specific interaction studies have been performed in humans. In preclinical studies SonoVue did not interact with the action of aspirin in vitro, or with the action of antihypertensive drugs (captopril, propranolol, or nifedipine), heparin, isosorbide dinitrate, or digoxin in rats *in vivo*.

There was no apparent relationship with respect to occurrence of adverse events in the clinical studies for patients receiving various categories of the most common concomitant medications.

Adverse events summarized for patients receiving concomitant medications categorized by Level I terms (all terms included) and by Level II terms (selected terms based on sponsor review of type and frequency of concomitant medications received) were monitored. A summary of the adverse events in patients taking and not taking concomitant medication categorized by Level I terms and selected Level II terms is presented in **Table 23**.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No long-term animal studies were performed to evaluate the carcinogenic potential of SonoVue.

Table 23 : Summary of Adverse Events by Concomitant Medication - All Patients (N=5147), SonoVue

	Taking Concomitant Medication		Not Taking Concomitant Medication	
Concomitant Medication (All Level I and selected Level II Terms)	**N**	**No. (%) of Patients with Adverse Events**	**N**	**No. (%) of Patients with Adverse Events**
Alimentary tract and metabolism	2147	311 (14.5)	3000	224 (7.5)
Drugs used in diabetes	591	90 (15.2)	4556	445 (9.8)
Antiinfectives for systemic use	300	30 (10.0)	4847	505 (10.4)
Antineoplastic and immunomodulating agents	162	12 (7.4)	4985	523 (10.5)
Antiparasitic products, insecticides and repellents	12	2 (16.7)	5135	533 (10.4)
Blood and blood forming organs	1358	225 (16.6)	3789	310 (8.2)
Antithrombotic agents	1179	208 (17.6)	3968	327 (8.2)
Cardiovascular system	2781	407 (14.6)	2366	128 (5.4)
Cardiac therapy	1142	213 (18.7)	4005	322 (8.0)
Beta blocking agents	1320	227 (17.2)	3827	308 (8.0)
Dermatologicals	116	18 (15.5)	5031	517 (10.3)
Genito urinary system and sex hormones	274	49 (17.9)	4873	486 (10.0)
Musculo-skeletal system	373	71 (19.0)	4774	464 (9.7)
Nervous system	1214	235 (19.4)	3933	300 (7.6)
Respiratory system	431	105 (24.4)	4716	430 (9.1)
Sensory organs	97	21 (21.6)	5050	514 (10.2)
Systemic hormonal preparations, excl. Sex hormones and insulins	316	44 (13.9)	4831	491 (10.2)
Various	254	54 (21.3)	4893	481 (9.8)

7.6.2 Human Reproduction and Pregnancy Data

Reproduction studies have been performed in rats and rabbits at daily doses up to at least 17 times and 35 times the daily human exposure, respectively, based upon body surface area, and have revealed no evidence of impaired fertility or harm to the fetus due to SonoVue.

Because animal reproduction studies are not always predictive of human response, and there are no adequate and well-controlled studies in pregnant women, SonoVue should not be used during pregnancy unless the physician determines the benefit of the use of SonoVue-enhanced procedure exceeds the risk to the fetus, infant and/or mother.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SonoVue is administered to a nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

SonoVue has not been studied in any pediatric patient groups and the use of trans-pulmonary contrast for the indented indication in patients with suboptimal echocardiograms is unlikely to be indicated in a substantial number of patients across all pediatric age groups.

As a matter of fact, suboptimal image quality that may benefit from SonoVue-enhanced echocardiography is frequently seen in adult patients for assessment of left ventricular function and wall motion to diagnose or to evaluate a number of adult-related heart diseases or conditions; however, suboptimal echocardiographic image quality is not a major problem in the pediatric population because of the relatively low prevalence of obesity and other conditions affecting echocardiographic image quality (such as chronic obstructive pulmonary diseases).

For the planned SonoVue NDA submission, (b) (4)

Overdose, Drug Abuse Potential, Withdrawal and Rebound

As shown in **Table 24**, for the 5239 subjects in the Completed Studies (healthy volunteers and patients) with exposure to SonoVue, the mean total volume administered was 10.32 mL (range 0.2 to 161.3 mL). This includes subjects who received multiple bolus doses of SonoVue in crossover studies as well as infusion dosing. Approximately 2500 subjects received total doses of >5 mL and 1200 subjects received total doses of >10 mL.

Since there have been no cases of overdose reported to date, neither signs nor symptoms of overdose have been identified.

SonoVue is only administered intravenously by medical personnel; the product is not available outside of healthcare facilities, such as hospitals or imaging centers. Therefore, the risk of incidental ingestion by patients, especially by children, is negligible.

Since there have been no cases of overdose reported to date, neither signs nor symptoms of overdose have been identified.

SonoVue is only administered intravenously by medical personnel; the product is not available outside of healthcare facilities, such as hospitals or imaging centers. Therefore, the risk of incidental ingestion by patients, especially by children, is negligible

Table 24 : Exposure to Study Agent (Healthy Volunteers and Patients), All Completed Studies, SonoVue

Total Volume SonoVue Administered (mL)	
N	5239
Mean (SD)	10.32 (14.435)
Median	4.80
Range (Minimum, Maximum)	(0.2, 161.3)
Cumulative Dose Categories	
≤1 mL	228 (4.4%)
>1 to 5 mL	2468 (47.1%)
>5 mL to 10 mL	1336 (25.5%)
>10 mL to 50 mL	1091 (20.8%)
>50 mL	116 (2.2%)

.Additional Submissions / Safety Issues

4-Month Safety Update

A supplemental 4-Month Safety Update was provided that included the results of Studies BR1-133 and BR1-129 integrated into the overall safety database as of January 31, 2012. Results for the 5 ongoing studies presented in the *Original NDA ISS* were not available as of the cut-off date for this safety update (January 31, 2012). No clinical trials have been completed during the period of October 1, 2011 to January 31, 2012. In this report, postmarketing surveillance (PMS) data is also updated as of January 31, 2012.

Two clinical trials continued to enroll patients between October 1, 2011 and January 31, 2012. A total of 99 patients with focal liver disease were dosed with SonoVue for the characterization of focal liver lesions in Studies BR1-128 and BR1-130.

Post-marketing surveillance based on sales statistics, with each unit sold representing one patient exposed to SonoVue, an estimated (b) (4) patients were exposed to SonoVue from October 1, 2011 through January 31, 2012. A total of 19 of these patients reported serious adverse reactions (reporting rate: (b) (4)). Of the 19 new serious adverse reaction cases, 13 were allergy-like or anaphylactoid in nature and 8 were cardiac-related as determined either solely by the Reporter, or by an internal medical review performed by Bracco.

No fatal outcomes were reported among the (b) (4) patients newly exposed to SonoVue during the 4-month period following the submission of the *Original NDA ISS*.

One patient experienced anaphylactic shock, considered to be related to SonoVue administration, and recovered completely after 28 days. Three weeks after the recovery, the patient died due to cardiac disease.

A literature search was performed on January 31, 2012 to identify any newly published (between October 1, 2011 and January 31, 2012) supportive evidence of the safety of intravenous SonoVue administration during echocardiography and non-cardiac ultrasound studies. This search yielded 10 articles, 8 of which were considered to be relevant and were included among the Non-Cardiac Population articles. No new information was published for patients within the Cardiac Population. No new safety concerns were raised in 8 recently published articles for Non-Cardiac Population as no adverse events were reported.

The updated numbers of unique subjects who received SonoVue and control agents in All Completed Studies are presented by category of study in **Table 25**.

Table 25 : Summary of Completed SonoVue Studies Included in Pooled Safety Database

Population	*Original NDA ISS*				*4-Month Safety Update*			
	No. of Studies	No. of Treated Subjects			No. of Studies	No. of Treated Subjects		
		SonoVue[a]	Control Only	Total		SonoVue[a]	Control Only	Total
All Completed Studies	70	5275	162	5437	72	5341	162	5503
Healthy Volunteers[b]	8	128	30[c]	158	8	128	30[c]	158
All Patients	62	5147	132	5279	64	5213	132	5345
Cardiac Population	24	1769	126[d]	1895	24	1769	126[d]	1895
Macrovascular Population	9	555	0	555	9	555	0	555
Microvascular Population	26	2785	0	2785	27	2815	0	2815
Special Patient Populations	3	38	6[c]	44	4	74	6	80

a Received SonoVue only or SonoVue plus control in crossover studies; included as SonoVue subjects in all summary data displays.
b Clinical pharmacokinetics and pilot efficacy studies in non-patient volunteers.
c Saline.
d Albunex and/or saline.

For this 4-Month Safety Update, a total of 5381 subjects were enrolled in the studies; 35 subjects discontinued prior to receiving SonoVue. Of the 5341 subjects who received SonoVue, 5057 (94.7%) completed the studies, while 284 (5.3%) discontinued prematurely (17 for adverse events, 4 for loss to follow-up, 37 for withdrawal of consent, 2 for protocol violations, 222 for other reasons [such as no treatment (including no surgery or no radio-frequency ablation)], and 3 with no reason specified). Up-dated disposition of subjects is summarized in **Table 26.**

Table 26 : Disposition of Subjects (Healthy Volunteers and Patients), All Completed Studies, SonoVue

Number of Subjects	*Original NDA ISS*	*4-Month Safety Update*
Enrolled (signed informed consent)	5315	5381
Discontinued Prior to Receiving Study Agent	35	35
Withdrawal of consent	7	7
Protocol violation	4	4
Other	24	24
Received Study Agent	5275 [a]	5341 [a]
Completed Study	5002 (94.8%)	5057 (94.7%)
Prematurely Discontinued	273 (5.2%)	284 (5.3%)
Adverse event	16 (0.3%)	16 (0.3%)
Lost to follow-up	4 (0.1%)	4 (0.1%)
Withdrawal of consent	37 (0.7%)	37 (0.7%)
Protocol violation	2 (<0.1%)	2 (<0.1%)
Other [b]	211 (4.0%)	222 (4.2%)
No reason specified	3 (0.1%)	3 (0.1%)

A summary of adverse events for All Completed Studies is presented in **Table 27**. Although the total number of patients dosed has increased, the percentage of incidence remains the same; therefore, there appears to be no significant change to the safety profile of SonoVue.

The most frequently reported adverse event was headache (109 subjects, 2.0%), followed by nausea (47 subjects, 0.9%), chest pain (33 subjects, 0.6%), chest discomfort (30 subjects, 0.6%), and injection site pain (26 subjects, 0.5%). All other adverse events occurred at a frequency of <0.5%. The adverse events experienced most frequently (>0.5%) by the 5341 subjects in All Completed Studies are summarized in **Table 28.** No notable difference is observed between adverse events reported in the *Original NDA ISS* and those reported in this 4-Month Safety Update.

All of the recorded terms for adverse reactions were additionally reviewed for appropriateness of body system assignment and for possible consolidation of multiple entries into single descriptive terms. The resulting incidences are provided in **Table 29**. The observed rates of adverse reactions are similar to those reported in the *Original NDA ISS*.

Table 27 : Summary of Adverse Events, All Completed Studies (Healthy Volunteers and Patients), SonoVue

	Original NDA ISS		*4-Month Safety Update*	
	N=5275		N=5341	
Category	**Total**	**Related[a]**	**Total**	**Related[a]**
No. (%) of Subjects with at least 1 AE	572 (10.8)	303 (5.7)	576 (10.8)	305 (5.7)
No. (%) of Subjects with at least 1 Serious AE	21 (0.4)	3 (0.1)	21 (0.4)	3 (0.1)
No. (%) of Subjects who Discontinued due to AEs	16 (0.3)	7 (0.1)	16 (0.3)	7 (0.1)
No. (%) of Deaths	7 (0.1)[d]	0	7 (0.1)[d]	0
No of AEs[b]	931	491	935	493
No. (%) of Subjects with at least 1 Non-serious AE by Intensity:[c]	555 (10.5)	300 (5.7)	559 (10.5)	302 (5.7)
Mild AEs	446 (8.5)	260 (4.9)	449 (8.4)	262 (4.9)
Moderate AEs	100 (1.9)	39 (0.7)	101 (1.9)	39 (0.7)
Severe AEs	9 (0.2)	1 (<0.1)	9 (0.2)	1 (<0.1)

[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.
[b] Multiple occurrences of the same adverse event in a subject are counted individually.
[c] If a subject experienced more than 1 non-serious adverse event, the subject was counted only once at the maximum intensity.
[d] One additional patient, who experienced 2 serious adverse events during the clinical trial, was reported to have died outside of the protocol-defined adverse event reporting window for Study BR1-071. One other death occurred in a patient who died of myocardial infarction before receiving SonoVue in Study BR1-020.

Table 28 : Adverse Events by System Organ Class Reported in >0.5% of the Subjects, All Completed Studies (Healthy Volunteers and Patients), SonoVue

	Original NDA ISS		*4-Month Safety Update*	
System Organ Class /	**No. (%) of Subjects (N=5275)**		**No. (%) of Subjects (N=5341)**	
Preferred Term	**Total**	**Related[a]**	**Total**	**Related[a]**
No. (%) of Subjects with at least 1 AE	572 (10.8)	303 (5.7)	576 (10.8)	305 (5.7)
Gastrointestinal Disorders				
Nausea	47 (0.9)	29 (0.5)	47 (0.9)	29 (0.5)
General Disorders/Administration Site Conditions				
Chest discomfort	30 (0.6)	16 (0.3)	30 (0.6)	16 (0.3)
Chest pain	33 (0.6)	9 (0.2)	33 (0.6)	9 (0.2)
Injection site pain	26 (0.5)	20 (0.4)	26 (0.5)	20 (0.4)
Nervous System Disorders				
Headache	109 (2.1)	59 (1.1)	109 (2.0)	59 (1.1)

[a] Includes definite, probable, possible, doubtful, unknown, and missing relationship.

Table 29 : Adverse Reactions Reported in ≥0.5% of Adult Subjects Who Received SonoVue in Clinical Trials

System Organ Class / Preferred Term	*Original NDA ISS* No. (%) of Subjects (N=5275)	*4-Month Safety Update* No. (%) of Subjects (N=5341)
Number of Subjects with Any Adverse Reaction	303 (5.7)	305 (5.7)
Gastrointestinal Disorders		
Nausea	29 (0.5)	29 (0.5)
General Disorders and Administration Site Disorders		
Injection Site Reaction[a]	46 (0.9)	46 (0.9)
Nervous System Disorders		
Headache	59 (1.1)	59 (1.1)

[a] Includes application site paraesthesia (1), infusion site oedema (1), injection site coldness (2), injection site discomfort (1), injection site erythema (2), injection site hematoma (1), injection site pain (20), injection site paraesthesia (4), injection site swelling (2), injection site warmth (12).

No notable difference is observed between adverse events reported in the *Original NDA ISS* and those reported in this 4-Month Safety Update.

Effects of Ultras*ound Exposure at High Mechanical Index after SonoVue Administration*

Several studies were performed in animals to demonstrate the safety of SonoVue with concurrent exposure to ultrasound at high power, expressed as mechanical index (MI).

In 7 out of 8 non-anesthetized dogs no effect was observed during exposure of the heart to ultrasound at various levels of mechanical index (up to 1.2) with concurrent administration of SonoVue (0.1, 0.3 and 1 mL/kg).

Histopathological examination of organs in rats after an intravenous injection up to 5 mL/kg and exposure to ultrasound at various mechanical index values was carried out in the Sprague- Dawley rat. In this study, 10 s after starting the ultrasound exposure the animals were injected with either SonoVue (1 or 5 mL/kg) or saline. In rats sacrificed 1 h after exposure, some minimal areas of blood suffusion within the pulmonary alveoli or close to the mesenteric blood vessels were observed microscopically. The incidence and grade of these findings in the various experimental groups and their presence in the saline treated groups show that they are not related to the administration or the dose of SonoVue. No other histopathological lesions, which could be attributed to the treatment of SonoVue and ultrasound exposures, were observed.

The results from the 2 continuous ECG clinical studies (BR1-112 and BR1-113) support the results from preclinical animal studies; administration of SonoVue at doses of 0.1 or 0.5 mL/kg does not appear to cause prolonged cardiac repolarization

in patients with CAD undergoing 2D echocardiography with a wide range of MI settings – from low (0.4-0.5), to medium (0.7-0.8), to high (1.5-1.6).

8 Postmarket Experience

SonoVue was first approved in Europe in 2001. It has been registered in a total of 36 countries worldwide and is currently marketed in 25 countries. It is recommended to be administered using a (b) (4) single vial per investigation (doses: 2.0 mL for endocardial border detection (b) (4) repeated once if necessary). Denominators are estimated from sales statistics, with each unit sold representing a patient exposed to the agent. Experience from post-marketing surveillance of the estimated (b) (4) patients exposed to SonoVue from April 1, 2001 through September 30, 2011 during the market use of this product shows a total of 246 cases of serious adverse reactions (reporting rate: (b) (4)) considered to have some kind of relationship to the administration of SonoVue (probable, possible, or unlikely).

SonoVue for intravenous use is currently approved in 36 countries for:

- Opacification of cardiac chambers
- Enhancement left ventricular endocardial border deliniation
- Enhancement echogenicity of blood for:
  - Doppler of Macrovasculature
    - Cerebral arteries
    - Extra-cranial carotid arteries
  - Doppler of Microvasculature
    - Vascularity of liver
    - Vascularity of breast

The reporting rate of serious adverse reactions in the last ten years of SonoVue marketing has remained fairly constant, (See **Figure 7**)

Figure 7 : SAE Reporting Rate in Last 10 years of SonoVue Marketing

Appendices

9.1 Literature Review/References

According to the Sponsor, the total number of patients included in the 87 publications that have safety information reported is 41,871, of whom, 12,232 underwent echocardiography examinations for cardiac indications reported in 20 publications and 29,639 underwent ultrasound examinations for non-cardiac indications reported in 67 publications. Overall from these published reports, the rate of adverse events in cardiac patients receiving SonoVue during rest and stress echocardiography is 0.64%.

Comparable results were also reported in a recently published meta-analysis [2] for all-cause mortality after the use of contrast agents for echocardiography. The cumulative incidence of all cause mortality in the contrast group was 0.34% (726/11,162) compared to 0.9% (45, 970/5, 078, 666) in the non-contrast group.

9.2 Labeling Recommendations

The Sponsor provided a proposed labeling for SonoVue. The DMIP is currently reviewing their proposal and will be recommending a number of revisions to insure that the finalized label clearly and accurately describes the prescribing information health care providers require to safely administer this drug.

9.3 Advisory Committee Meeting

At the 2011 CRDAC, safety of all USC Agents were reviewed, concerns were raised regarding safety of USCA and the members agreed:

- Validity of retrospective studies was questionable
- Premier Database and propensity score analyses had limitations
- Absence of significant pulmonary hemodynamic effects by USCA

Based on CRDAC assessment, the members arrived at the following conclusions:

- Understanding of safety risk of USCA was evolving
- Risks exist, but events appear to occur randomly
- Re-assessments led to reduced scope of Black Box warnings

2 Khawaja OA, Shaikh KA, Al-Mallah MH. Meta-analysis of adverse cardiovascular events associated with echocardiographic contrast agents. Am J Cardiol. 2010;106(5):742-7.

Following the CRDAC meeting, Bracco requested guidance from the FDA for going forward with their upcoming submission. Meeting with the FDA in 2011, 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]

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

/s/

SCHELDON KRESS
08/24/2012

ALEXANDER GOROVETS
08/24/2012
The primary review is complete.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203684 **Applicant: Bracco** **Stamp Date: 12-20-2011**

Drug Name: **Sonovue (pending re-naming)** **NDA/BLA Type:** **Suspension for injection** [Sulfur hexafluoride (SF6) microspheres w phospholipid shell]

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			Hybrid CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			Clinical Efficacy 2.7.3 Clinical Safety 2.7.4
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			Deaths in 2.7.4 Abstracts provided Not linked to CRF
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			Section 1.14.1
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			Section 5.5.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			Section 5.5.5.3.27
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			Brief Sections 2.5.6 & 1.16
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	√			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	√			BR1-001 (24) BR1-002 (20) BR1-005 (36) BR1-007 (10) BR1-019A (143) BR1-019B (121)ldon
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1BR1-019A Indication: Lt ventricular EBD - Dose-ranging	√			Section 5.3.5.1.3

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 BR1-019B Indication: Lt ventricular EBD - Dose-ranging Confirmatory Study BR1-013 Crossover Dose-ranging				Section 5.3.5.1.3 Section 5.3.5.1.3
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	√			Section 5.3.5.4.1
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	√			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			> 5000 subjects
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			Section5.3.5.3
OTHER STUDIES					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			Section 1.9.1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	Section 2.7.4.7
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			Not linkable from Lists and Tables
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			By Studies in Section 5.3.5.4
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			Section 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			BR1-019A BR1-019B BR1-013

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Recommendations:

1. Inspection of Sponsor's product relative to verification of data quality, integrity and GPC compliance.
2. Request a world-wide safety update focusing on deaths, serious adverse events and discontinuations of drug.

Scheldon Kress	February 16, 2012
Reviewing Medical Officer	Date
Alex Gorovets	February 16, 2012
Clinical Team Leader	Date

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

/s/

SCHELDON KRESS
02/17/2012