



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 May 2014
EMA/454283/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SonoVue

International non-proprietary name: sulfur hexafluoride

Procedure No. EMEA/H/C/000303/II/0025

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bracco International B.V. submitted to the European Medicines Agency on 24 July 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
SonoVue	sulfur hexafluoride	See Annex A

The following variation was requested:

Variation requested	Type
C.I.4 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of section 4.3 of the SmPC in order to delete the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease and to insert information on these patient populations into section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Pierre Demolis

1.2. Steps taken for the assessment

Submission date:	24 July 2013
Start of procedure:	25 August 2013
Rapporteur's preliminary assessment report circulated on:	7 October 2013
Rapporteur's updated assessment report circulated on:	21 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	13 November 2013
Rapporteur's assessment report on the MAH's responses circulated on:	29 November 2013
2 nd Request for supplementary information and	18 December 2013

extension of timetable adopted by the CHMP on:	
MAH's responses submitted to the CHMP on:	16 January 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	03 February 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	13 February 2014
3 rd Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	21 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 April 2014
CHMP opinion (via written procedure)	29 April 2014

2. Scientific discussion

2.1. Introduction

SonoVue is an ultrasound contrast agent (USCA). It contains sulphur hexafluoride (a gas) as microbubbles in suspension in a liquid, after made up into a solution (kit including one vial of gas and powder and one pre-filled syringe containing 5 ml of solvent). It is intravenous administered.

Sonovue was centrally approved in Europe in 2001. Other USCA in European centralised procedure are Luminity (perflutren) and Optison (perflutren, authorised on 1998). SonoVue is approved in 36 countries world-wide and marketed in 25 countries world-wide.

SonoVue is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio. SonoVue should only be used in patients where study without contrast enhancement is inconclusive:

- Echocardiography: SonoVue is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation.

- Doppler of macrovasculature: SonoVue increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal to noise ratio. SonoVue increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment.

- Doppler of microvasculature: SonoVue improves display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.

In May of 2004, SonoVue was temporarily suspended from the European market for the cardiac indication, based on reports of 3 cases of adverse events with fatal outcome and temporal relationship to SonoVue administered for echocardiography in patients with underlying severe cardiac disease. SonoVue remained on the market for use in extra cardiac indications. In July 2004, the Committee for Medicinal Products for Human Use (CHMP) recommended the re-instatement of the cardiac indication, but required the introduction of contraindications to avoid the use of the product in patients with recent acute coronary syndrome (ACS) or clinically unstable ischaemic cardiac disease, including: evolving or on-going

myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of electrocardiogram [ECG], laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders. Since 2004, additional information on the safety of SonoVue has become available from both clinical trials and post-marketing surveillance, with estimated exposure of over 2 million patients.

Current contra-indications are:

- *known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue.*
- *patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or on-going myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders.*
- *patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.*
- *pregnancy and lactation.*

In the currently submitted type II variation, the applicant is requesting the deletion in Section 4.3 of the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease and the insertion of these patient populations into Section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. These changes are also reflected in revised wording for the PIL.

The principle of this deletion was subjected to an EMA scientific advice on 20 September 2012. In conclusion, the CHMP recommended to the Applicant to submit a type II variation where the proposed change to the SmPC would be supported by the following:

- A summary and discussion of similarities and differences in pharmaceutical composition of registered USCAs that could possibly be relevant to risk of adverse CV outcome.
- All relevant (comparative) haemodynamic or other (clinical) pharmacology data that could address the question of potential underlying mechanism for CV risk. The Applicant should explore options for additional investigations in a sensitive model.
- Meaningful observational/epidemiological / pharmacovigilance data that is relevant to the specific patient population at hand (in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease) and would enable a comparison between this agent and other similar USCAs (e.g. patient matching).

It was not considered meaningful to expect that a prospectively planned comparative safety trial of feasible size will be sufficiently sensitive and informative to support a decision to remove the mentioned contraindications from the label.

Additional revisions to Product information (SmPC/PIL) in accordance to QRD v.9 are also proposed, following consultation and agreement by EMA.

Note

Narrative summaries for the 3 post-marketing surveillance cases with fatal outcome and temporal relationship to SonoVue which led to the temporary suspension of the product from the European market are described below.

- **Case BRO-005943 (Germany, 2002)** describes a 69-year-old male patient with history of anterior and posterior myocardial infarction, percutaneous transluminal coronary angiography (PTCA) and stent placement in left anterior descending coronary artery (LAD) was admitted for an angiographic follow-up, which showed 3-vessel disease (occlusion of right coronary artery, RCA, high grade restenosis in distal LAD stent, and several stenoses in left circumflex artery, LCx). A new revascularization of LAD in-stent-restenosis was performed successfully. The following day, the patient was feeling well except for an unusual restlessness and before undergoing echocardiography with SonoVue. About 4-5 minutes following the 2nd injection of 2-2.5 mL SonoVue, the restlessness increased, heart rate decreased from 90 bpm to 50 bpm, blood pressure also decreased, accompanied by cold sweat. An anaphylactic shock was initially suspected and the patient treated accordingly, but the patient's conditions continued to deteriorate. An emergency coronary angiography performed after the SonoVue study showed a complete, new thrombotic reocclusion of the LAD-stent and PTCA was performed successfully with restored TIMI III Flow. The patient's blood pressure was recorded as approximately 100 mmHg and cardiac rhythm was normalized. The patient was transferred to ICU with intra-aortic balloon pump. Later at ICU, the patient developed bradycardia and a ventricular escape rhythm and despite treatment, the patient died of a cardiogenic shock. The fatal outcome was considered by the reporter to be related to the underlying severe cardiac disease and unrelated to the administration of SonoVue.
- **Case BRO-006772 (Germany, 2003)** concerns a 49-year-old male patient with 3-vessel coronary artery disease and a history of multiple myocardial infarctions, severe reduction of left ventricular function (ejection fraction 31%) due to a new, recent acute anterior myocardial infarction. The patient underwent multiple percutaneous coronary interventions (PCIs) of the LAD, but no revascularization procedure was performed on the significant, 80% to 90% narrowing of the LCx and RCA. One month after PCI, he underwent a rest echocardiogram with SonoVue to assess left ventricular function. The exam was eventless. The patient became unconscious after the exam while getting up from the examination table. No ECG was available at the onset of event. During the event the ECG showed asystole, blood pressure and pulse were not measurable. The patient was immediately treated with cardiopulmonary resuscitation measures. Despite treatment, the patient developed pulseless electrical activity followed by ventricular fibrillation. The patient was announced dead 40 minutes after the resuscitation was started. No autopsy was performed. Due to the temporal relationship, a role of SonoVue in the development of the initial hypotension was considered possible.
- **Case BCM-000767 (Italy, 2003)** describes a 51-year-old patient suffering from 40% occlusion of the common trunk and recent anterior myocardial infarction treated with PTCA of LAD. The patient developed a bundle branch block. An echocardiogram with SonoVue was performed one month later. About 2 minutes after SonoVue injection, the patient reported throat burning and back pain. Echocardiogram showed asystole. Despite the reanimation procedures and pharmacological treatment with adrenaline, cortisone and fibrinolytic agents, the patient died. The autopsy showed a 90% stenosis at the ostium of the common trunk and a thrombus completely occluding the distal common trunk. The autopsy report indicated the cause of death as "presence of thrombus occluding common trunk". Based on the autopsy report, the reporting physician excluded a role of SonoVue in the onset of the reported event and

subsequent fatal outcome and considered the observed events related to the thrombotic occlusion of the common trunk.

2.2. Quality aspects

SonoVue is formulated as a 25 mg sterile, non-pyrogenic lyophilized powder in a septum-sealed vial. The gas phase in the vial is SF₆, an innocuous gas. The lyophilized powder is made of a combination of pharmaceutical grade polyethylene glycol (PEG) 4000, phospholipids, and palmitic acid. Phospholipids from chemical synthesis were selected for their high chemical purity and low pyrogenic potential. In SonoVue, the phospholipid component is a mixture of distearoylphosphatidylcholine (DSPC) and dipalmitoyl phosphatidylglycerol sodium (DPPG.Na).

The microbubble dispersion is prepared before use by injecting 5 mL of sodium chloride 0.9% w/v solution for injection, USP, into the content of the vial. The vial is then shaken for a few seconds to provide a homogeneous dispersion. Each mL of SonoVue dispersion contains 8 µL SF₆ in the microbubbles. The desired volume of the dispersion can be drawn into a syringe at any time up to 6 hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microbubbles.

Final formulation (marketed in approved countries)

<u>Ingredient</u>	<u>Amount</u>
PEG, molecular weight 4000	4.91 mg per mL
Phospholipids (DSPC/DPPG Na 1:1 w/w)	0.076 mg per
mL Palmitic acid	0.008 mg per
mL	
SF ₆	approx. 8 L per mL

Table 1 Formulation of SonoVue Used in Clinical Studies

Ingredients	Marketed Formulation 25 mg
Active ingredient: SF ₆	sufficient quantity to 1 atmosphere
Other ingredients: PEG, molecular weight 4000 DSPC DPPG.Na Palmitic acid	24.56 mg 0.19 mg 0.19 mg 0.04 mg
<i>Data source: Individual clinical study report</i>	

Table 2 Comparison of the Pharmaceutical Composition of the 3 USCA's

	SonoVue^a	Luminity^b	Optison^c
Manufacturing technology	Lyophilisation	High speed agitation	Sonication
Main components concentrations	Gas: SF ₆ Phospholipids: • DSPC 38 mg/mL • DPPG.Na 38 mg/mL • Palmitic acid 8 mg/mL	Gas: C ₃ F ₈ Phospholipids: • DPPC 401 mg/L MPEG5000DPPE 304 mg/mL • DPPA 45 mg/mL	Gas: C ₃ F ₈ Protein: HSA, 10 mg/mL
Other components	Saline, Macrogol 4000	Saline, glycerin, propylene glycol	Saline, caprylic acid N-acetyltryptophan,
Approved single dose	2 or 2.4 mL	0.1-0.4 mL	0.5-3 mL
HSA or phospholipid injected	168 or 201 mg	75-300 mg	5-30 mg
Max dose approved	4 or 4.8 mL	1.6 mL	8.7 mL
Maximum HSA or phospholipid injected	336-401 mg	1200 mg	87 mg
Bubble characteristics: Mean diameter (range) Bubble concentration Distribution Maximum size	1.5 - 2.5 μm 1.5 – 5.6 x 10 ⁸ /mL 90% <6 μm; 99% <10 μm 20 μm	1.1 – 2.5 μm 6.4 x 10 ⁷ – 1.2 x 10 ¹⁰ /mL 98% <10 μm; 2% >10 μm	2.5 – 4.5 μm 5-8 x 10 ⁸ /mL 93% <10 μm 32 μm
Bubbles injected per single dose	3 – 13 x 10 ⁸	0.06 – 48 x 10 ⁸	5 – 8 x 10 ⁸
Bubbles injected / max approved dose	6 – 26 x 10 ⁸	0.8 – 192 x 10 ⁸	43 – 70 x 10 ⁸
Gas volume/mL	8 μL/ mL	150 μL/mL	0.19 mg/mL
<p><i>DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine; MPEG5000DPPE, N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine; C₃F₈, perflutren; DPPA, 1,2-dipalmitoyl-sn-glycero-3-phosphatidic acid; HSA, human serum albumin; MTD, maximum tolerated dose.</i></p> <p><i>a 8 μL/mL powder and solvent for dispersion for injection</i> <i>b 150 μL/mL solution for dispersion for injection or infusion c 0.19 mg/mL dispersion for injection</i> <i>Data Source: FDA Briefing Package, FDA Advisory Committee Meeting June 2008; Luminity/Definity, EU SmPC, US Package Insert; Optison, EU SmPC, US Package Insert.</i></p>			

Conclusion on pharmaceutical comparability

There are some differences among the agents:

- SonoVue and Luminity are both based on phospholipid-stabilized microbubbles. Unlike SonoVue and Luminity, Optison microbubbles are stabilized by protein (human serum albumin, HSA).
- SonoVue shows a more controlled bubble size distribution than Luminity and Optison.
- Maximum bubble size is smaller for Luminity and SonoVue (20 microns [μ]), than for Optison (32 μ).
- SonoVue uses a lesser amount of phospholipids and contains lower gas volumes than Luminity.

Based on information provided in Table above based on the pharmaceutical composition of the three approved USCAs (Optison, Luminity and SonoVue), similarities and differences among the agents are summarized below:

- All three agents in the marketplace have in common a particulate structure. They differ with regard to composition (human serum albumin vs phospholipids) and concentrations (750 µg/mL vs 84 µg/mL for Luminity and SonoVue, respectively).
- Risk of gas embolism is none or remote at the approved doses because:
 - The number of bubbles and the volumes of gas administered with approved doses are comparable. Actually, only minute amounts of gas are administered with an imaging dose, especially with SonoVue (16 to 38 µL vs approx. 240 µL with Luminity and 0.1-1.7 mg with Optison);
 - Maximum bubble size is 20 µm for Luminity and SonoVue, 32 µm for Optison;
 - Mean bubble sizes range from 1.5 to 4.5 µm. This range provides strong echo enhancement over a broad frequency range (2-10 MHz);
 - Coalescence of bubbles does not occur for any agent;
 - While bubble numbers in the order of $3-13 \times 10^8$ in each milliliter for SonoVue seems very large, the number of capillaries in the human body is many times larger (estimated at 40×10^9). Microscopic examination of the capillary bed in animal models such as the hamster cheek pouch or rat spinotrapezius muscle do not reveal any bubbles after administration to the animal of doses equivalent to the human imaging dose. Doses administered need to be at least 100 or 200 times the equivalent human dose before the presence of bubbles in capillaries can be observed. Of note, the SonoVue microbubbles always exhibited microvascular transit properties similar to those of the red blood cells.
- All agents make use of low solubility gases in order to achieve longer persistence. SF₆ and C₃F₈ are non-toxic and not metabolized. They are exhaled within minutes, also by patients with restrictive lung disease.
- SonoVue and Luminity are comparable since both are based on phospholipid-stabilized microbubbles. However; SonoVue shows a more controlled bubble size distribution, makes use of less phospholipids and contains lower gas volumes.
- Cardiovascular risk is not expected to depend on predictable adverse reactions to any of the components or agents' composition.
- Potential hypersensitivity to any of the components of these USCAs cannot be excluded, with the potential for unpredictable, serious hypersensitivity reactions.

2.3. Clinical Pharmacology aspects

The clinical pharmacology studies included in this application are aimed at providing information that could reasonably exclude underlying mechanisms of cardiovascular risk in the general population and, more important, in critically ill patients.

To this purpose, the following studies are included:

- **Study BR1-112:** single-blind, placebo-controlled, randomized, 3-way crossover comparison of the

effects on QTc interval of single IV injections of two bolus doses of SonoVue (0.1 and 0.5 mL/kg) with matched volumes of placebo in patients with documented coronary artery disease (CAD); 0.1 and 0.5 mL/kg correspond to 7 and 35 mL in a 70-kg person, i.e., approx. 3.5 and 17.5 times the recommended single dose of SonoVue in echocardiography (2 mL, i.e., approx. 0.03 mL/kg in a 70-kg person).

- **Study BR1-113:** single-blind, placebo-controlled, randomized, 4-way crossover study to compare the effects on QTc of 0.1 mL/kg IV bolus of SonoVue and placebo in conjunction with continuous heart insonation mode at mechanical index (MI) settings of 0.4–0.5 and 1.5–1.6 in CAD patients.
- **Study BR1-016:** placebo-controlled, randomized study in patients with congestive heart failure (NYHA class II-III), Ejection Fraction (EF) < 45% and referred for right cardiac catheterization, echocardiography and multi-gated (MUGA) radionuclide angiography.
- **Study BR1-133:** single-blind, placebo controlled, study to evaluate the hemodynamic effects of SonoVue in subjects (at least 30) with and without pulmonary hypertension, scheduled for pulmonary artery catheterization. Pulmonary hypertension was defined as mean pulmonary arterial pressure ≥ 25.0 mmHg, according to the ACCF/AHA 2009 expert consensus document.
- **Study BR1-022:** randomized, single-blind, crossover comparison of the effects on respiratory function of 4 mL IV bolus of SonoVue or placebo in patients with moderate-to- severe COPD; 4 mL is two times higher than the single dose of SonoVue approved for its use in echocardiography.
- **Study BR1-036:** primarily conducted to evaluate the pharmacokinetics of SF6 following intravenous administration of 0.3 mL/kg SonoVue in patients with severe restrictive lung disease due to DIPF, the evaluation of safety was also a primary objective of the study (ECG, vital signs, oxygen saturation).

The final Clinical Study Reports for 5 of this 6 clinical pharmacology studies have been submitted in previous applications (BR1-112, BR1-113, BR1-016, BR1-022, and BR1-036). The final report for study BR1-133 has not been submitted previously and the full final report is included in this submission.

Table 3 Clinical study results

Study	Evaluation	Results
BR1-112 BR1-113	Continuous 12-lead ECG collected from 3 hours predose to 12 hours postdose following each administration of study agent	<ul style="list-style-type: none"> • For all ECG parameters, the magnitude of the changes from baseline was similar for SonoVue and placebo • SonoVue did not show any significant effects on ventricular repolarization <ul style="list-style-type: none"> - at single, bolus IV doses 3.5-17.5 times higher than the recommended dose for endocardial border delineation - at high mechanical index and continuous insonation

BR1-016 BR1-133	PVR, MPAP, PCWP monitored by right heart catheterization predose and up to 10 min postdose. Cardiac function and O ₂ saturation were measured.	<ul style="list-style-type: none"> • Oxygen saturation was within normal in all cases • No significant changes in cardiac output or signs of cardiac function worsening • No significant effects on pulmonary hemodynamics after either SonoVue or placebo: <ul style="list-style-type: none"> - no difference between SonoVue and placebo - no difference between the 2-mL and 4-mL SonoVue doses • Pulmonary hemodynamics are not influenced by the administration of ultrasound contrast agents in subjects with either normal or elevated mean pulmonary artery pressure • Elevations in pulmonary artery pressure induced by ultrasound contrast agents in animal studies do not appear to translate to humans • Results in the SonoVue clinical trial were similar to the results in the Optison and Luminity trial
BR1-022	Pulmonary function (FVC, FEV1 and FEF _{25-75%}) measured at time points up to	No effect of SonoVue on pulmonary function tests, oxygen saturation, ECG, or laboratory tests was observed in patients with COPD
BR1-036	Oxygen saturation measured through 1 hour post dose.	No changes or clinically meaningful trends observed in oxygen saturation or other safety parameters in patients with DIPF
BR1-124	Blood samples to assess the presence of specific antibodies and clinical and anamnestic data	<ul style="list-style-type: none"> • No differences between the 2 groups were observed between case subjects (subjects with a previous serious hypersensitivity reaction to SonoVue) and Control subjects (subjects exposed to the administration of SonoVue with no occurrence of any adverse reaction). • Mechanistic basis for rare unpredictable hypersensitive reactions to SonoVue, is still largely unknown.
<p><i>DIPF, diffuse interstitial pulmonary fibrosis; PVR, pulmonary vascular resistance; MPAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; FEV, forced expiratory volume; FVC, forced vital capacity; FEF, forced mid-expiratory flow.</i></p> <p><i>Data source: Individual Clinical Study Reports (BR1-112, BR1-113, BR1-016, BR1-133, BR1-022, BR1-036)</i></p>		

MAH's Conclusion from supportive clinical studies

Clinical pharmacology studies did not show any significant effect, including after high dose administration or during continuous insonation at high mechanical index, on the following:

- pulmonary hemodynamics;
- pulmonary function;
- blood pressure and other vital signs;
- oxygen saturation;
- cardiac function;
- electrocardiographic parameters; and
- laboratory test results.

Cardiovascular risk does not seem to depend on predictable adverse reactions to the administration of SonoVue, as demonstrated in several patient populations with chronic condition affecting cardiac and pulmonary functions.

The mechanistic basis for rare unpredictable hypersensitive reactions to SonoVue, other USCAs and other types of contrast agents (used in radiographic or magnetic resonance exams) is still largely unknown. Potential hypersensitivity to one of the components of USCAs cannot be excluded, with the potential for unpredictable, serious hypersensitivity reactions.

In conclusion, based on data from SonoVue clinical pharmacology studies, no significant risks are identified for ventricular repolarization or for pulmonary hemodynamics or function after administration of SonoVue in patient populations with several types of chronic clinical conditions with compromising effects on the pulmonary and cardiovascular systems

2.4. Clinical Safety aspects

Methods – analysis of data submitted

Safety assessments of SonoVue include data from SonoVue clinical studies in humans; post-marketing surveillance from launch (26 March 2001) to 31 December 2012; and reports in the published literature with relevant safety data.

Results

1) Clinical trials

Safety data from 75 completed studies have been pooled to provide the integrated safety database for the SonoVue clinical program conducted in North America, Europe, and Asia as of 31 December 2012. A total of 6469 subjects have participated in the 75 completed studies included in the Integrated SonoVue Safety Database; 6307 subjects received SonoVue (either exclusively or in addition to control agent in cross-over studies) and 162 subjects received control agent only.

Adverse Reactions Reported with the Use of SonoVue in Clinical Trials

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 (Table O). Study agent-related adverse events were reported by 331 subjects (5.2%). The majority of events were mild and resolved without sequelae. Only 9 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 8 deaths (0.1%) were reported in all completed clinical studies conducted with SonoVue since 1993. All 8 deaths were considered to be unrelated to study agent by both the Investigators and the MAH. Deaths occurred in both cardiac and non-cardiac studies. In particular:

- 1 patient had procedural complications during percutaneous coronary intervention (PCI) and 1 other 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 are, 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.

Further details about the deaths, including a narrative summary for each of the patients who died after receiving at least one administration of SonoVue during a study are provided in the Summary of Clinical Safety, Section 2.7.4 of this CTD.

Table 4 Summary of Adverse Events in All Completed Studies in the Pooled Safety Database (Healthy Volunteers and Patients Who Received SonoVue)

Category	N=63	
	Total	Related
No. (%) of Subjects with at least 1 AE	675 (10.7)	331 (5.2)
No. (%) of Subjects with at least 1 Serious AE	27 (0.4) ^b	5 (0.1)
No. (%) of Subjects who Discontinued due to AEs	23 (0.4)	12 (0.2)
No. (%) of Deaths	8 (0.1) ^c	0
No of AEs ^d	1064	531
No. (%) of Subjects with at least 1 Non-serious AE by Intensity: ^e	653 (10.4)	326 (5.2)
Mild AEs	521 (8.3)	281 (4.5)
Moderate AEs	123 (2.0)	44 (0.7)
Severe AEs	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 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.

Data source: 12-Month Safety Update Table 4.1.

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%.

A complete presentation of the adverse events that were reported in the completed studies (Healthy Volunteer and Patient populations) is provided in the Summary of Clinical Safety, Section 2.7.4 of this CTD.

Overall MAH's Conclusions from Clinical Trials

SonoVue has been shown to be safe and well tolerated with minimal risk to patients.

In clinical trials, the overall incidence of adverse events was relatively low (10.7% overall, 5.2% investigational product-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. Serious adverse events occurred in 0.43% of patients and only 0.08% of events were considered to be of some relationship to the administration of SonoVue (probable, possible, or unlikely). No product- related deaths were reported within MAH-sponsored trials.

The overall incidence of adverse events and the type of most frequently reported adverse events is similar among SonoVue, Optison and Luminity.

2) 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 01 April

2001 to 31 December 2012. Denominators are estimated from sales statistics, with each unit sold representing a patient exposed to the agent.

During market use (01 April 2001 through 31 December 2012), an estimated 2,447,083 patients have been exposed to SonoVue.

Adverse Reactions

Of the estimated 2,447,083 patients exposed to SonoVue during the market use of the product, adverse events for which both Reporter and MAH causality assessments did not exclude causal relationship to the administration of SonoVue were spontaneously reported for 719 cases (reporting rate: 0.0294%). A total of 322 cases (reporting rate: 0.0132%) of the 719 cases were classified as serious and 397 non-serious (reporting rate: 0.0162%). Adverse reactions (causality could not be ruled out by either the Reporter or MAH) were reported in 702 cases (reporting rate: 0.0287%), of which 307 were serious (reporting rate: 0.0126%) and 395 were non-serious (reporting rate: 0.0161%).

Table 5 Post-Marketing Surveillance: Comparison of Adverse Reactions by System Organ Class Spontaneously Reported from 01 April 2001 to 31 December 2012

	Number and Reporting Rate of Patients					
	Serious		Non-Serious		Total	
Total No. of Patients with Adverse Reactions	307	0.012546	395	0.016142	702	0.028687
Cardiac disorders	77	0.003147	17	0.000695	94	0.003841
Ear and labyrinth disorders	0	0	2	0.000082	2	0.000082
Eye disorders	4	0.000163	11	0.000450	15	0.000613
Gastrointestinal disorders	9	0.000368	71	0.002901	80	0.003269
General disorders and administration site conditions	32	0.001308	279	0.011401	311	0.012709
Immune system disorders	176	0.007192	26	0.001062	202	0.008255
Injury, poisoning and procedural complications	0	0	12	0.000490	12	0.000490
Investigations	40	0.001635	19	0.000776	59	0.002411
Metabolism and nutrition disorders	1	0.000041	0	0	1	0.000041
Musculoskeletal and connective tissue disorders	4	0.000163	12	0.000490	16	0.000654
Nervous system disorders	50	0.002043	66	0.002697	116	0.004740
Pregnancy, puerperium and prenatal conditions	1	0.000041	0	0	1	0.000041
Psychiatric disorders	2	0.000082	8	0.000327	10	0.000409
Renal and urinary disorders	4	0.000163	5	0.000204	9	0.000368
Respiratory, thoracic and mediastinal disorders	53	0.002166	25	0.001022	78	0.003187
Skin and subcutaneous tissue disorders	45	0.001839	89	0.003637	134	0.005476
Surgical and medical procedures	3	0.000123	19	0.000776	22	0.000899

Vascular disorders	61	0.002493	26	0.001062	87	0.003555
<p><i>NOTE: Patients are counted once for each system organ class; the same patient may be reported for more than one system organ class.</i></p> <p><i>* = Estimated.</i></p> <p><i>Data source: post-marketing surveillance database.</i></p>						

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 the MAH excluded the causality relationship to the administration of SonoVue. The SonoVue serious cases reporting rate per year through 31 December 2012 remains low (ranging from 0.0110% to 0.0196%) and stable across the last 11.5 years of Pharmacovigilance surveillance. This by-quarter analysis excludes the first 6 months of marketing [01 April 2001 to 30 September 2001], during which only 470 patients were exposed to SonoVue; in this period 2 adverse reaction case reports were received, 1 serious case and 1 non-serious case.

Serious Cases with Allergy-like Reactions

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 the MAH, an additional 53 ADR cases should be medically classified as allergy-like events.

Therefore, a total of 229 out of 307 patients with serious ADRs 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 31 December 2012. In most cases allergy-like events presented an onset within a few minutes from the injection of the product.

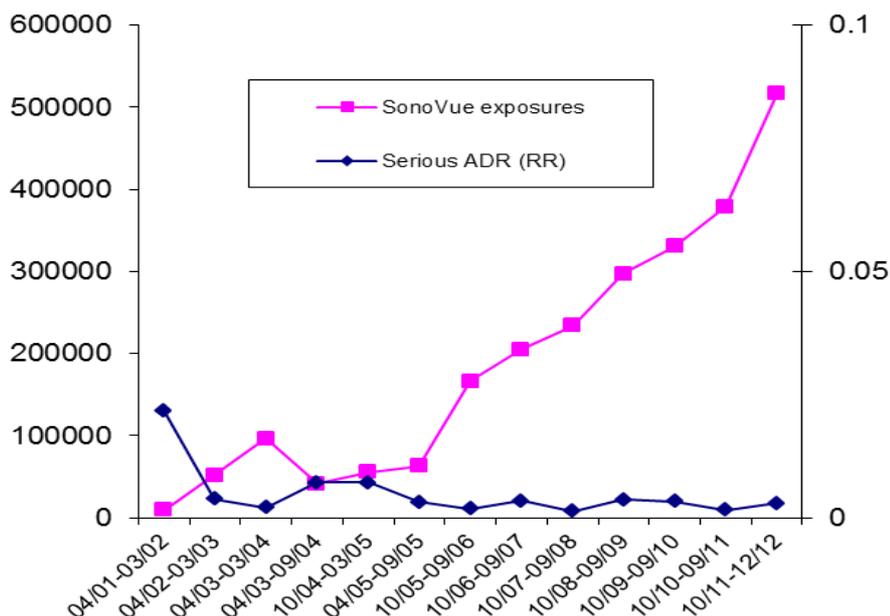
In 53 of the 229 serious allergy-like reactions, hypotension (preferred terms: hypotension, blood pressure decrease, blood pressure immeasurable, syncope, presyncope, circulatory collapse, and pulse pressure decrease) was reported at the onset of the allergy-like reaction. The severity of hypotension could range from a reduction of a few mmHg in systolic blood pressure and diastolic blood pressure to non-measurable levels.

The overall incidence of serious allergic reactions is estimated to be in the order of 1:10,000 exposed to SonoVue as of 31 December 2012. In most cases allergy-like events presented an onset within a few minutes from the injection of the product.

Serious Cardiac Reactions

A total of 94 patients experienced 106 cardiac-related ADRs during the post-marketing surveillance period of 01 April 2001 to 31 December 2012. Of these 94 patients, 77 patients (0.0031% of exposed patients) experienced serious cardiac-related adverse reactions. After a medical review of all PTs 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.

Figure 1 Reporting Rate of Serious Cardiac-Related Adverse Drug Reactions in the Last 11.5 Years of SonoVue Marketing



During the post-marketing surveillance period of 01 April 2001 to 31 December 2012, a total of 118 patients (0.0048% of exposed patients) experienced serious cardiac-related adverse reactions. Seventy-one (71) of these cases (60.2%) were associated with allergy-like/anaphylactoid reactions.

Post-marketing Surveillance Death Cases

Of the 2,447,083 patients exposed to SonoVue during the market use of the product (01 April 2001 to 31 December 2012, the data cut-off for this document), 11 cases of fatal outcome have been reported (reporting rate: 0.0004%, a figure that compares favourably with the risk for fatal events reported for iodinated contrast agents that is approximately 0.001% to 0.003%). The association with the administration of SonoVue could not be ruled out in 9 of the 11 cases, whereas there was no relation to SonoVue reported for the remaining 2 cases. In all death cases, the poor underlying conditions of the patients played a major role in the fatal outcome: 6 patients had severe underlying CAD with ongoing or recent acute myocardial infarction, and history of multiple coronary interventions and left ventricular dysfunction; 1 patient had limited information on his cardiac condition except an apical left ventricular thrombus, which is often associated with myocardial infarction and is a condition characterized by substantial mortality rate; 3 patients had advanced stage cancer; 1 patient was a long-term smoker with a history of hypertension who shortly before SonoVue exposure was having a fever and was suspected to have liver abscesses with significantly elevated alpha fetoprotein and possible gastrointestinal bleeding.

In addition to these 11 patients, 2 other patients experienced unrelated serious adverse events of 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.

Of the 2,447,083 patients exposed to SonoVue during the market use of the product (01 April 2001 to 31 December 2012, the data cut-off for this document), 11 cases of fatal outcome have been reported. The association with the administration of SonoVue could not be ruled out in 9 of the 11 cases. In all death cases, the poor underlying conditions of the patients played a major role in the fatal outcome: 6 patients had severe underlying CAD with on-going or recent acute myocardial infarction, and history of multiple coronary interventions and left ventricular dysfunction; 1 patient had limited information on his cardiac condition except an apical left ventricular thrombus, which is often associated with myocardial infarction and is a condition characterized by substantial mortality rate; 3 patients had advanced stage cancer; 1 patient was a long-term smoker with a history of hypertension who shortly before SonoVue exposure was having a fever and was suspected to have liver abscesses with significantly elevated alpha fetoprotein and possible gastrointestinal bleeding.

MAH's Comparison of Post-marketing Surveillance amongst the 3 USCA's

In post-marketing surveillance data collected from 2001 to 2012, with close to 2,447,083 patients exposed, the reporting rate of serious adverse events for SonoVue is approximately 1 in 10,000 exposures and is comparable to that of Optison and Luminity. No major trends or significant changes in the reporting rate of serious adverse events have been observed over time. Comparison of post-marketing surveillance data gathered in the period 2008-2010 show similar reporting rates among the three approved USCA's.

Table 6 Comparison of Safety Data from Post-Marketing Surveillance for USCA's (Data from 2008 to 2010)

	SonoVue ^(a)	Luminity ^(b,c)	Optison ^(b,d)
Timeframe	2008 to 2010	2008 to 2010	2008 to 2010
Estimated Exposure	906,634	1,083,000	55,000
Serious Adverse Events	109 (0.012%)	169 (0.016%)	6 (0.011%)
Fatal Cases	4 (0.0004%)	10 (0.0009%)	0

a Post-marketing surveillance data available as of 31 December 2010.

b Data for Luminity (Definity) and Optison are from briefing documents for the respective compound presented at the Joint.

Meeting of the CRDAC and the DSaRM hosted by the United States FDA in May 2011.37

c Luminity was not on the EU market for approximately 3 years. The product was re-introduced to the market on 15 June 2011.

d Optison was not on the market from June 2009 to July 2010.

MAH's Conclusions from Post-Marketing Surveillance

Experience from post-marketing surveillance of the estimated 2,447,083 patients exposed to SonoVue from 01 April 2001 through 31 December 2012 during the market use of this product shows:

- A total of 307 cases of serious adverse reactions (reporting rate: 0.0126%) considered to be related to the administration of SonoVue;

- 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 very low (14/2,447,083 exposed patients; 0.0006%) and favourably comparable with the risk for fatal events reported for iodinated contrast agents (approximately 0.001%);

MAH's Comparison of Adverse Reactions Reported for the 3 USCAs

It has been demonstrated in numerous clinical studies of the 3 registered USCAs that cardiovascular risk with the use of USCAs is not expected to depend on predictable adverse reactions to any of the individual components or the composition of the agents.

Table below displays overall incidence rates in clinical trials for the 3 products available to date. SonoVue has been studied in more patients and has a lower percentage of patients reporting adverse events, and a lower rate of adverse events where the causal relationship to the investigational product could not be ruled out.

Table 7 Safety in Clinical Trials: SonoVue vs Other Ultrasound Contrast Agents

	SonoVue ^(a)	Luminity ^(b)	Optison ^(c)
Patients who Received Study Agent	617	398	279
% Patients with Adverse Events	10.3%	26%	16.8%
% Patients with Related Adverse	4.9%	7.6%	Not reported
% Patients with Serious Adverse	0.4%	0.85%	0.4%
Most Frequent Adverse Events	<p><u>>0.5%</u></p> <p>Headache (2.0%) Nausea (0.9%) Chest pain (0.8%) Chest discomfort (0.5%)</p>	<p><u>>1%*</u></p> <p>Fatigue, headache, dyspnea, back pain, nausea, flushing, dizziness</p>	<p><u>>2%</u></p> <p>Headache (5.4%) Nausea/vomiting (4.3%) Warm sensation or flushing (3.6%) Dizziness (2.5%)</p>

* Treatment-related Adverse Events

a Completed clinical trials in patients data as of 31 December 2012.

b 2008 Advisory Committee Meeting Briefing Package: Definity (Perflutren Lipid Microsphere). From FDA

website: <http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-4369b1-04.pdf>. Accessed April 26, 2011. c

Optison (Perflutren protein-Type A microspheres injectable suspension) August 2012 Full Prescribing Information from <http://www.optisonimaging.com>. Accessed on 22 March 2013.

<http://www.optisonimaging.com>. Accessed on 22 March 2013.

3) Retrospective Epidemiological Studies

Retrospective Epidemiological Study BR1-132 in SonoVue

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 SonoVue 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 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 COPD, 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.

Data from participating sites were abstracted by Investigator/Site personnel and included patient elements such as age, gender, race, admitting diagnosis, treatment received (i.e., contrast agent), and mortality status. The primary study variable was in-hospital mortality (within the same day of echocardiography procedure and/or the following calendar day). The secondary study variables included patient demographic, baseline characteristics, co-morbidity conditions, and other risk factors.

Univariate Analysis

The incidences of in-hospital mortality were estimated for each study group. The crude odds ratio with the 95% CI for comparison of in-hospital mortality between the 2 groups was derived from univariate logistic regression model. The p-value from Wald chi-square test of logistic regression analysis was presented comparing the incidence of in-hospital mortality between the 2 groups.

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

This was a non-randomized observational study, therefore, the distribution of patient baseline characteristics and risk factors were likely to vary systematically between the SonoVue and Control groups since assignment of study group was not randomly assigned but rather passively observed. Propensity score matching method was used to control for the imbalance in observable covariates between the 2 study groups and thus to reduce potential biases due to confounding factors in the estimation of treatment effect on the same day or next day mortality among study populations. The intent of propensity analysis was to mimic the conditions of a randomized trial such that patients were similar in every measurable respect except for treatment (SonoVue or Control) allocation.

The first step was to calculate the propensity score for each patient from the logistic equation. Propensity score was the probability that each patient would get SonoVue-enhanced echocardiography and this probability was predicted using the following stepwise multivariate logistic regression model that included all observed variables from demographic, baseline characteristics, co-morbid conditions, risk factors, and hospital status. Covariates considered with best predictive power in the model for propensity score were: age, gender, admission to ER, CCU, respiratory distress syndrome, coronary syndrome, pulmonary heart

disorder, recent coronary artery intervention, severe rhythm disorder, worsening heart failure, anti-coagulant treatment, dyslipidemia, and muscular-skeletal disorder.

Control patients who met inclusion criteria were used as the control base for matching the SonoVue patients. For each SonoVue patient, 1 matched control patient will be assigned who showed the smallest difference in propensity scores using nearest neighbor matching method with greedy-matching algorithm.

To compare in-hospital same day and/or the following calendar day mortality between matched SonoVue and Control patients, a conditional logistic regression model was applied to estimate treatment effects. Propensity score was included in the final conditional logistic regression model. Adjusted odds ratio was estimated along with 95% confidence intervals presented.

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 (CCU), 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

Adverse events were collected whenever such information was available in patients' medical records. For the purpose of this retrospective study, an adverse event was defined as any untoward medical occurrence reported in the patient's medical records which had occurred immediately after the start of the echocardiography within the same day of echocardiography procedure and/or the following calendar day. Any untoward medical occurrence that occurred outside of this period was not collected.

A blinded medical review of all major adverse events was performed by 2 physicians to confirm major events of interest (e.g., new major cardiac events, worsening of cardiac condition, and hypersensitivity reactions). Major adverse events were identified as:

- Hypersensitivity/Anaphylactoid reaction
- Hypotension
- Chest Pain
- Acute MI
- Cardiac Arrhythmia requiring intervention and including:
 - Third degree atrioventricular block
 - Frequent multifocal R on T PVCs
 - Bigeminy PVCs

- Sustained and non –sustained ventricular tachycardia (VT)
- Ventricular Fibrillation (VF)
- Q-T prolongation
- New onset of Atrial Fibrillation
- Severe Bradycardia
- Cardiac arrest
- Pulmonary embolism

The incidences of death and major adverse events were estimated for each study group. The crude odds ratio with the 95% CI for comparison between the 2 groups was presented and the difference between 2 groups was tested by Fishers Exact test. 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.

Retrospective Epidemiological Studies of Other Contrast Agent Use in Critically ill Patients

Retrospective epidemiological studies in critically ill patients have also been conducted for the other 2 USCA's using a propensity-matched database. A comparison of the methods used amongst the 3 products is presented in Table below. The results were the same 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 8 Comparison of Results for Retrospective Epidemiological Studies Using 3 USCA's in Critically ill Patients

	SonoVue		Luminy		Optison	
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		Premier's Perspective (billing database)		Premier's Perspective (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	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 (%)

Day or Next Day)	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)	
<i>CE-Echo=Contrast-enhanced echocardiography</i>						
<i>OR = Contrast odds of mortality relative to non-contrast odds of mortality estimated with unconditional multivariate logistic regression models.</i>						

Literature Review: Studies of the Safety and Effectiveness of USCAs in the Critically Ill Population

With the current contraindications imposed on the use of SonoVue in the critically ill patient population, little to no evidence of its safety and effectiveness is available in published scientific literature. However, an extensive literature search was performed identifying additional retrospective and prospective studies with SonoVue and other USCAs published during the time period of 01 January 1996 to 31 December 2012 that confirmed and extended the safety findings in the critically ill patient population. This search was performed utilizing PubMed, a service of the US National Library of Medicine, Medline, CancerLit, Derwent Drug File, Biosys Preview, International Pharmaceutical Abstracts, Embase, Biobase, Biological Abstracts, CAB Abstracts, CSA Life Science Abstracts, Cochrane Database for Systematic Reviews, and the Cochrane Controlled Trials Register. The search was conducted using the following key terms: (SonoVue OR Sulfur hexafluoride OR sulphur hexafluoride OR BR1 OR BR-1 OR Definity OR Optison OR perflutren OR ultrasound* OR ultrason* OR ultrasound contrast agent) AND (echocardio* OR cardiac disease OR critically ill patients OR acute coronary syndrome OR clinically unstable ischemic cardiac disease OR AMI OR myocardial infarct* OR acute cardiac failure OR typical angina at rest within last 7 days OR coronary artery intervention OR PTCA OR cardiac ablation OR class III/IV cardiac failure OR class III cardiac failure OR class IV cardiac failure OR ventricular remodeling OR ventricular arrhythmia OR severe emphysema OR pulmonary emboli OR severe pulmonary hypertension OR adult respiratory distress syndrome OR respiratory failure OR apical thrombus OR unstable angina OR intensive care unit OR ICU OR cardiac care unit OR CCU). The search was limited to "human". No other limits were applied.

A total of 752 unique references were identified in the search results. All articles identified in the search were reviewed against the inclusion and exclusion criteria listed below.

Eligibility Criteria

Publications that met all the following inclusion criteria were included in the safety literature summary:

- Original publication of a clinical study in human subjects with prospective or retrospective enrolment
- Any of the 3 USCAs were administered intravenously during an echocardiography examination
- Information on safety (e.g., adverse events, side effects, complications) related to the administration of any of the 3 USCAs was reported.

Publications that did not meet the inclusion criteria or met the following exclusion criteria were excluded from the safety literature summary:

- Study was performed in non-human subjects (e.g., phantom, in vitro or animal studies);
- An USCA was not administered or was not administered intravenously;
- No safety information related to the use of any of the 3 USCAs was reported;

- Results were from MAH-sponsored clinical trials (these are already included in the Integrated Safety Database from completed clinical studies of SonoVue); or
- Publications were other than study reports, such as review articles, author correspondence, editorials, letter-to-editor, case reports or conference or scientific meeting abstracts that have no or insufficient data of study population, study methodology and results or if there is a lack of completeness in the reports.

Results

Among the 752 unique references identified in the literature search, 20 publications met the inclusion criteria. Eight of the publications were focused on the safe use of USCA in the critically ill patient population. These publications are briefly presented in the following Table and summarized below.

Table 9 Safety of Contrast in Critically ill Patients

Study Authors	Year	No Contrast TTE (n)	Contrast TTE (n)	Population	Study Design USCA	Primary Endpoint	Results
Gaibazzi et al ⁴	2011	500	500	Emergency Department	Retrospective Single center SonoVue	Adverse events	No deaths, myocardial infarctions, sustained arrhythmias, or severe AEs; no significant difference in AEs between SonoVue and an historical control group
Kusnetzky et al ⁵	2008	12,475	6196	Inpatients, ICU	Retrospective Single center Definity	Acute mortality (1 day)	0.37% without and 0.42% with contrast; p=0.6
Wei et al ⁶	2008	780,243	78,383	Inpatients, outpatients, ICU, ACS	Retrospective Multicenter Optison/Definity	Adverse events	Serious adverse events, probably related: 0.01% in contrast group; No deaths
Exuzides et al ⁷	2010	11,600	2900	Critically ill; AMI; Pulmonary hypertension	Retrospective Multicenter Optison	Acute mortality (1 day)	Odds Ratio 1.18 95% CI 0.82-1.71 p=0.37
Abdelmoneim et al ⁸	2010	10,270	6164	Inpatients, outpatients, Pulmonary hypertension	Retrospective Single center Optison/Definity	Mortality (≤ 72 hrs) with respect to RVSP	Odds ratio for death 1.06 in patients with RVSP ≥ 50 mmHg

Gabriel et al ⁹	2009	- -	2267	Pulmonary hypertension	Retrospective Single center Optison/Definity	Adverse events Mortality	No serious adverse events No deaths
Main et al ¹⁰	2009	19,871	19,318	Critically ill, Mechanical ventilation	Retrospective Multicenter Optison/Definity	Survival Mortality rate	Short term mortality rate: 2.98% for noncontrast TTE vs. 2.30% for contrast TTE
Main et al ¹¹	2008	4,242,712	58,254	Inpatients Heart failure, ACS, AMI, Ventricular arrhythmia, Respiratory failure, Pulmonary hypertension	Retrospective Multicenter Definity	Acute mortality (1 day)	Patients who received contrast had 24% decreased risk of mortality
<i>ACS, acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; ICU, intensive care unit; RVSP, right ventricular systolic pressure; TTE, transthoracic echocardiography; USCA, ultrasound contrast agent.</i>							

Gaibazzi et al conducted a single-center retrospective study of the safety of SonoVue in contrast-flash replenishment dipyrimadole-atropine (DASE) in 500 Emergency Department patients with chest pain but with normal ECGs and troponin I levels. The interval between the chest pain event and the DASE procedure was <5 days. Adverse were recorded during and immediately after DASE and at a 24-hour follow-up with each patient. The possible presence of arrhythmia after DASE was specifically determined by reviewing the following data sources for each patient: 12-lead ECG data acquired during each stage of the stress protocol, all the digitally- stored flash-replenishment clips, and the real-time ECG on the echo monitor during the DASE procedure. Adverse events were compared with an historical control group of 500 patients who received DASE within the preceding year in which contrast was not used; in this group, the interval between the event of chest pain and the DASE procedure was up to 5 days.

No fatalities, myocardial infarction, or acute coronary syndromes and no study-related severe AEs were reported during the DASE procedure or during the 24 hour follow-up. Troponin I did not rise to above normal level for any patient in the subgroup tested (n=95). All AEs were mild or moderate and self-limiting or promptly resolving after aminophylline administration or with atropine administration (for vagal reaction). Common AEs (reported in >1% of patients) included mild headache and dry mouth (common side effects of dipyrimadole-atropine), premature ventricular complexes, vasovagal reaction without loss of consciousness, and supraventricular premature beats. Uncommon AEs (reported in >1% of patients) were hypotension, atrial fibrillation/flutter, supraventricular tachycardia, fatigue, non-sustained ventricular tachycardia (1 patient), second-degree atrioventricular (AV) block; left bundle branch block, vomiting, and pain at injection site. There were no significant differences between the SonoVue and the control group in AEs. However, the authors stated that the need to use an historical group for control patients was a limitation of the study.

Kuznetsky et al studied acute mortality in a total of 18,671 hospitalized patients who underwent clinically indicated transthoracic echocardiographic examination with or without the use of a contrast agent (Definity). Incidence of death within 24 hours was compared by chi-square test between the contrast-enhanced and unenhanced procedures. The vital status within 24 hours of each echocardiogram was obtained retrospectively from medical records and the Social Security Death Master File. Of the 18,671 patients, 12,475 patients had undergone unenhanced echo, and 6,196 had undergone contrast-enhanced echocardiogram. Results indicated that there were 72 deaths reported within 24 hours in the total patient population of 18,671. Of the 72 deaths, 46 (0.37%; 46/12,475 patients) were in the group of patients

echocardiograms without contrast, and 26 deaths (0.42%; 26/6196 patients) were among the patients in the contrast group. There were no deaths within 1 hour of echocardiogram. There was no statistical difference between the 2 groups. In addition, the authors discovered that in a random sampling from both groups, patients who underwent contrast enhanced studies exhibited higher clinical acuity and more significant comorbidities. In conclusion, this study indicated that there was no increased mortality risk associated with Definity-enhanced echocardiographic examination in hospitalized patients, despite evidence for higher clinical acuity and more comorbid conditions in patients undergoing contrast-enhanced studies.

In a multicenter retrospective study, *Wei et al* demonstrated the incidence of severe adverse events following exposure to USCA during echocardiographic examination. The data were derived from a total of 66,164 doses of Definity and 12,219 doses of Optison with rest and stress echocardiographic procedures during a period of 4.5±2.4 years. More than 10,000 doses of contrast were used in patients with acute chest pain of suspected cardiac origin or critically ill patients in intensive care unit (ICU) settings. A total of 8 serious reactions were reported as being probably related to Definity, 4 of which were consistent with anaphylactic reactions. All of the severe reactions occurred in outpatients. No deaths were reported. The limitation of the study was the adverse events were reported not under research protocols with a systematic approach, but as part of routine clinical care. It is unlikely that severe adverse events were missed, but mild symptoms may have gone unreported. This study demonstrated that the USCA during echocardiography have a good safety profile in a large number of patients evaluated in a wide variety of settings including the critically ill.

A comparison of mortality in critically ill hospitalized patients undergoing echocardiography with and without USCA has been reported in a retrospective multi-center study by *Exuzides et al*.⁷ A total of 2,588,722 patients who underwent echocardiographic exam were identified by a hospital service-level database of which 22,499 received Optison during echocardiography. Of the 22,499 patients, only 2,900 of them met the critically ill criteria which included the patients with acute myocardial infarction, arrhythmia, pulmonary embolism, respiratory failure, heart failure, pulmonary hypertension and emphysema. Comorbidities, demographic factors, levels of care, mechanical ventilation status were used as variables in constructing the propensity score matching to control the differences between the critically ill patients who underwent echocardiography with or without contrast. Critically ill patients who underwent contrast-enhanced echocardiography were matched to 4 control patients who underwent an echocardiographic exam without contrast. Before matching, contrast patients showed greater morbidity than non-contrast patients (Deyo-modified Charlson comorbidity index score 2.45 vs. 2.25, $p < 0.0001$). These differences significantly were reduced following the propensity score matching as an indicator of well-balanced groups.

The primary outcome for this study was all-cause, same-day mortality, the secondary outcome was all-cause, same-day or next day mortality. A total of 2,900 critically ill patients with contrast enhanced echocardiography were compared to 11,600 patients with non-contrast echocardiography as a control group. There were 167 same-day deaths in the study, 38 from the contrast group and 129 from the control group. There were no statistically significant differences between the contrast patients and the matched control patients for same day all-cause mortality (adjusted odd ratio 1.18, 95% CI 0.82 to 1.71; $p = 0.37$). There was 267 same day or next day deaths in the study, 62 from the contrast group and 205 from the control group. No statistical difference was found between the contrast and matched control groups for same-day or next day all-cause mortality (adjusted odds ratio: 1.22; 95% CI: 0.91 to 1.64; $p = 0.18$).

Furthermore, the same day mortality was compared between the contrast group and non-contrast control matched in three different subgroups: patients who had mechanical ventilation, ICU patients without mechanical ventilation and CCU patients without mechanical ventilation. None of the sub-groups showed a statistically significant difference in same-day mortality. There were 108 same-day deaths in the

mechanical ventilation subgroup, 22 in the contrast group and 86 in the non-contrast control group reported (adjusted odds ratio: 0.83, 95% CI 0.49 to 1.42; $p=0.51$).

There were 30 same-day deaths in the ICU subgroup, 9 in the contrast and 21 in the non-contrast control group (adjusted odds ratio: 2.168, 95% CI 0.89 to 5.27; $p=0.09$).

In the CCU subgroup, 3 patients in the contrast group and 8 in the non-contrast control group totaling up to 11 same-day deaths were reported (adjusted odds ratio: 1.42, 95% CI 0.38 to 5.36; $p=0.61$).

The study had some limitations. It was an observational study and treatment selection was non-random. The discrete time of death was not available in the Premier database, only the day of death was recorded.

Overall, there were no statistical differences identified in same-day or next day mortality in the critically ill patients who underwent echocardiography with contrast versus patients who did not receive contrast. These findings were also confirmed in higher risk patient subgroups as the patients in ICU's, CCU's and patients who have mechanical ventilation. In critically ill patients undergoing echo with contrast, there was no increase in mortality compared with case-matched control patients who had echocardiographic exam without contrast.

Abdelmonemin et al addressed the safety of USCA use during stress echocardiography in patients with increased right ventricular systolic pressure (RVSP) as determined by the peak tricuspid regurgitant velocity. A total of 16,434 patients who had RVSP measured at rest to evaluate the safety of contrast in patients with pulmonary hypertension have been studied. Of those, 6164 patients (39% had exercise echo and 61% had dobutamine stress echo) have received contrast (Optison and Definity) for left ventricular opacification and the remaining 10,270 (60% exercise echo, and 40 % had dobutamine stress echo) did not receive contrast. The primary outcome of the study was the short term safety (<72 hours and <30 days) of the contrast agents that were given to the patients with elevated RVSP during echocardiographic examination. End points analysed were death (all-cause mortality) and myocardial infarction. The secondary outcome of the study was the long term safety of contrast agent use and the time to the event (death or myocardial infarction). In addition, all the documented adverse effects related to contrast agents and arrhythmias were reported. Analysis was done for resting RVSP with cut points of >35, >50 and >60 mmHg and tricuspid regurgitation velocities with cut points of >2.7 and >3.5 ms⁻¹, respectively. Contrast agent related adverse events only occurred in 0.98% (less than 1%) of patients. There were no significant differences were found between the contrast and non-contrast cohorts with respect to short term events in patients with RVSP >50 mmHg. Similarly, there were no significant differences between contrasts vs. non-contrast cohort for long term events. Furthermore, similar results were obtained with different RVSP and tricuspid regurgitation cut points.

This retrospective cohort study addressed the safety of USCA use during stress echocardiographic examination in patients with increased RVSP as determined by resting tricuspid regurgitant peak velocity. There were no differences in rates for death and myocardial infarct in the group who had undergone echocardiographic exam with contrast compared with those who had not received contrast, despite a higher incidence of clinical comorbidities in the contrast cohort. In conclusion, the use of contrast agents during echocardiography in patients with elevated RVSP was not associated with increased short term or long term rates of death or myocardial infarction.

Similarly, *Gabriel et al* also studied the safety of contrast agents (Optison and Definity) during echocardiography in patients with pulmonary hypertension. An accurate measurement of RVSP from contrast enhanced tricuspid regurgitation velocity was obtained in 3479 (35%) of total of 10,010 patients who had received contrast during echocardiographic exam. Mild pulmonary hypertension was documented in 1921 patients, and 346 patients had severe pulmonary hypertension. Within 24 hours of contrast administration, there was no documented cardiac arrest, anaphylaxis or sustained ventricular arrhythmia noted. Overall, in a total of 2267 patients with documented pulmonary hypertension who received USCAs

during echocardiography, no serious adverse events were noted. This study confirms the safety of ultrasound contrast use during echocardiography in patients with pulmonary hypertension.

Main et al studied retrospectively the safety of contrast agent use during echocardiography among critically ill patients including those who were mechanically ventilated in ICU setting. Of the 39,189 critically ill patients who had echocardiograms performed while in the ICU, 19,318 received contrast (Definity and Optison) and 19,871 did not. Short term mortality (<48 hours) rates were 2.98% in patients who had an echo without contrast, and 2.3% for patients who had echo with contrast. Multivariate logistic regression analysis revealed that short term mortality among critically ill patients was 23% less in patients who had received contrast. This multicenter retrospective large cohort study results have confirmed that transthoracic echocardiography with contrast is associated with higher 48-hour survival in critically ill patients in ICUs.

Further, *Main et al* assessed the short term (one day) mortality in a large multicenter cohort of hospitalized patients undergoing clinically indicated echocardiography with and without contrast agent. In this observational retrospective study, consecutive 4,300,966 patients who had undergone transthoracic rest echocardiogram were selected from United States hospitals participating in the Premier Perspective database. Of those 4,300,966 patients, 4,242,712 had echocardiography without contrast and remaining 58,254 with contrast. Mortality rates were 1.08% (45,789 of 4,242,712) for patients undergoing non-contrast studies and 1.06% (616 of 58,254) for patients undergoing contrast (Definity) enhanced echocardiography. There was no statistically significant difference between the two groups with respect to mortality rate. Multivariate logistic regression analysis revealed patients who had received contrast during echocardiography were 24% less likely to die within one day than patients who had not received contrast (adjusted odd ratio: 0.76, 95% CI 0.70 to 0.82).

MAH's Overall Conclusions from Retrospective Epidemiological Studies

The results of Study BR1-132 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).

The comparison among the 3 USCAs revealed that same-day and next-day mortality rates for contrast-enhanced echocardiography were either lower (SonoVue and Luminity) than or comparable (Optison) to that for non-contrast echocardiography.

The published literature confirms the safe use of contrast in critically ill patients (including but not limited to ACS, AMI, and severe pulmonary hypertension) as there were no statistically significant differences observed between those administered contrast and those not.

2.5 Changes to the Product Information

4.3 Contraindications

~~Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. SonoVue should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue.~~

~~SonoVue is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders.~~

SonoVue is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.

~~SonoVue should not be used in combination with dobutamine in patients with conditions suggesting cardiovascular instability where dobutamine is contraindicated.~~

The safety and efficacy of SonoVue have not been established in pregnant and lactating women therefore, SonoVue should not be administered during pregnancy and lactation (see Section 4.6).

4.4 Special warnings and precautions for use

ECG monitoring should be performed in high-risk patients as clinically indicated.

It should be emphasised that stress echocardiography, which can mimic an ischaemic episode, could potentially increase the risk of SonoVue utilisation. Therefore, if SonoVue is to be used in conjunction with stress echocardiography patients must have a stable condition verified by absence of chest pain or ECG modification during the two preceding days.

Moreover, ECG and blood pressure monitoring should be performed during SonoVue-enhanced echocardiography with a pharmacological stress (e.g. with dobutamine).

~~Care should be taken in patients with ischaemic cardiac disease because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions.~~

Use extreme caution when considering the administration of SonoVue in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions. SonoVue should only be administered to such patients after careful risk/benefit assessment and a closely monitoring of vital signs should be performed during and after administration

Emergency equipment and personnel trained in its use must be readily available.

In the event of an anaphylactic reaction, beta blockers (including eye drop preparations) may aggravate the reaction. Patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Caution is advised when SonoVue is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.

It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue.

Numbers of patients with the following conditions who were exposed to SonoVue in the clinical trials were limited, and therefore, caution is advisable when administering the product to patients with: acute endocarditis, prosthetic valves, acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent thromboembolism, and end-stage renal or hepatic disease.

SonoVue is not suitable for use in ventilated patients, and those with unstable neurological diseases.

In animal studies, the application of echo-contrast agents revealed biological side effects (e.g. endothelial cell injury, capillary rupture) by interaction with the ultrasound beam. Although these biological side effects have not been reported in humans, the use of a low mechanical index is recommended.

Pharmacovigilance system

Not reviewed

Risk management plan

The MAH has submitted an updated Risk Management Plan (version 8, dated 05 March 2014) in the context of the type II-25 variation. In this procedure, the applicant was requested to delete the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease in Section 4.3 and the insertion of these patient populations into Section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. These changes are also reflected in revised wording for the PIL. The CHMP recommended the submission of an amended RMP and educational material accordingly to the proposed changes of Section 4.3 and 4.4 of the SPC.

The RMP version 8 also includes changes requested by PRAC Rapporteur from preliminary PSUR No. 17 (covering the period between 01 Oct 2012 to 30 Sep 2013) and RMP version 7 Assessment report. Off-label use of SonoVue in the adult population has been removed from the important potential risk category. Although the MAH is continuing to monitor the off-label use of SonoVue, the risk minimisation measures are now more specifically directed to anaphylactic/anaphylactoid reactions in patients receiving SonoVue, including patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease

2.4.3. Discussion

Although there are differences in the pharmaceutical composition of the three USCAs approved in the EU, the safety and efficacy profile of these three products is very similar, as demonstrated by clinical and post-marketing surveillance data. SonoVue efficacy and safety is based on data from 75 clinical trials in 6307 subjects and post-marketing surveillance over 11.5 years of market use in an estimated 2.45 million patients. Hypersensitivity to any of the components of SonoVue, cannot be excluded, and there is potential for unpredictable, serious hypersensitivity reactions, including anaphylactoid reactions. Further, such reactions may lead to life-threatening conditions if they occur in critically ill patients. However, serious hypersensitivity reactions after SonoVue administration are rare (estimated occurrence of approx.

1 in 10,000 exposures) and suboptimal EBD and inaccurate assessment of LV function (global and regional wall motion assessment) and/or cardiac anatomy are frequent in this patient population. This may severely limit the diagnostic performance of TTE, the imaging modality that represents a fundamental investigation used in the initial and on-going management of patients in the critical care setting because it is non-invasive, provides easy access, anytime and any day, can be performed at the bedside of the patient, and can be repeated as often as needed for monitoring. The balance of benefit of SonoVue use compared with its risks is also positively affected by the availability of acute care skills and settings that can promptly and effectively recognize and manage serious adverse events.

Among critically ill patients, significant difficulties may limit optimal TTE imaging due to the complex and dynamic profile of critically ill patients in the ICU and emergency department. Many will be unable to assume an optimal position for imaging due to pain or inability to cooperate. Mechanical ventilation, lung disease, subcutaneous emphysema, surgical incisions, chest tubes and bandages are relatively common during critical illness and the percentage of suboptimal examinations in critically ill patients is reported to be at least twice that in the overall population referred for TTE.

Although optional non-invasive modalities (SPECT, MRI, CT angiography) may provide diagnostic accuracy and valuable and detailed data, all pose greater risk than TTE. Probably the most critical drawback is the time delay in obtaining the data needed for urgent risk assessment and treatment, but safety concerns including exposure to radioactive material and risky patient transportation to the nuclear/magnetic imaging department are also present. Further, if an imaging agent is used, these imaging modalities carry the same risk of rare, serious hypersensitivity reactions and the same risk of serious, life-threatening complications.

Transesophageal echocardiography (TEE) is another optional procedure and, like TTE, it provides high accuracy real-time bedside data. But TEE is an invasive technique, introducing significant risks associated with anaesthesia and manipulation of the inserted probe as well as certain imaging limitations.

As a result, TTE is the modality of choice for the diagnosis of cardiovascular disease in critical care settings and both EAE and ASE guidelines recommend the use of ultrasound contrast in ICU patients with suboptimal endocardial border delineation. Clinical studies and wide post-marketing use of SonoVue have categorically demonstrated its significant benefit in enabling accurate LV volumes and LVEF in patients with suboptimal non contrast images, including critically ill patients.

Conversion of suboptimal to optimal LV images translates to more efficient patient management including a reduction in the need for additional diagnostic procedures, unnecessary hospital admissions and more effective treatment regimens administered more expeditiously and can predict possible post-admission complications in these patients. Further, an accurate assessment of LV structure and function in these patients has additional prognostic value, which allows more accurate triage for preventive treatment for post-event complications. Hypersensitivity reactions were observed in SonoVue, including potentially serious anaphylactoid reactions, may be life threatening, the healthcare professional must be warned about the occurrence of these rare events.

The applicant provided a comprehensive review of available clinical safety data derived from 6 clinical pharmacology studies, 75 clinical trials in which 6307 subjects received Sonovue, post-marketing surveillance and retrospective epidemiological studies including 8 publications focused on the safe use of USCAs in the critically ill patient population.

Data from post-marketing surveillance (from 1 April 2001 to 31 December 2012 with an estimated number of patients of 2,447,083) indicated that a total of 118 patients (0.0048% of exposed patients) experienced serious cardiac-related adverse reactions. Seventy-one (71) of these cases (60.2%) were associated with allergy-like/anaphylactoid reactions. The overall incidence of serious allergic reactions is estimated to be in the order of 1:10,000 exposed to SonoVue as of 31 December 2012. In most cases

allergy-like events presented an onset within a few minutes from the injection of the product. Eleven cases of fatal outcome have been reported. The association with the administration of SonoVue could not be ruled out in 9 of the 11 cases. In all death cases, the poor underlying conditions of the patients played a major role in the fatal outcome: 6 patients had severe underlying CAD with on-going or recent acute myocardial infarction, and history of multiple coronary interventions and left ventricular dysfunction; 1 patient had limited information on his cardiac condition except an apical left ventricular thrombus, which is often associated with myocardial infarction and is a condition characterized by substantial mortality rate; 3 patients had advanced stage cancer; 1 patient was a long-term smoker with a history of hypertension who shortly before SonoVue exposure was having a fever and was suspected to have liver abscesses with significantly elevated alpha fetoprotein and possible gastrointestinal bleeding.

In this post-marketing surveillance data, the reporting rate of serious adverse events for SonoVue is approximately 1 in 10,000 exposures and is comparable to that of Optison and Luminity. No major trends or significant changes in the reporting rate of serious adverse events have been observed over time. Comparison of post-marketing surveillance data gathered in the period 2008-2010 show similar reporting rates among the three approved USCAs.

SonoVue is the only ultrasound contrast agent approved for use in stress echocardiography, i.e., in conjunction with the use of pharmacological stressors like dobutamine, a cardiac inotrope and chronotrope that increases heart rate and myocardial oxygen demand, or dipyridamole, a vasodilator that increases blood velocity and flow rate in normal vessels and less of a response in stenotic vessels. Both types of stressors induce local myocardial ischemia in CAD patients that may be visible on the echocardiogram as a regional wall motion abnormality. To accurately detect wall motion abnormalities, proper visualization of entire endocardium for every vessel territory, with complete delineation of the endocardial border, is critical for the detection and assessment of coronary artery disease.

Based on the information received from the reporters, four out of the 5 observed cases of severe cardiac arrhythmia did not occur in patients with any of the conditions in which current use of SonoVue is contraindicated, i.e., evolving or on-going myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, or severe rhythm disorders. Only in one case, occurred in a patient with dilated cardiomyopathy, it is not clear whether there was one of the conditions in which the use SonoVue was contraindicated, i.e., class III or IV cardiac failure. However, both SonoVue and dobutamine are contraindicated for use in patients with severe heart failure, and the risk of complications following dobutamine administration in patients with severe heart failure is high. Therefore, the MAH believes this patient did not actually suffer from severe heart failure, even if, following the stress echocardiographic procedure, the patient had a rapid deterioration of her conditions and eventually died 19 days after the stress echocardiographic procedure.

Of note is the fact that stress echocardiography with dobutamine is contraindicated in patients with conditions suggesting cardiovascular instability, such as unstable angina pectoris, recent myocardial infarction, stenosis of the main left coronary artery, haemodynamically significant outflow obstruction of the left ventricle including hypertrophic obstructive cardiomyopathy, haemodynamically significant cardiac valvular defect, Class III/IV cardiac failure, predisposition for or documented medical history of clinically significant or chronic arrhythmia, particularly recurrent persistent ventricular tachycardia, significant disturbance in conduction, acute pericarditis, myocarditis or endocarditis, aortic dissection, aortic aneurysm, inadequately treated / controlled arterial hypertension, obstruction of ventricular filling (constrictive pericarditis, pericardial tamponade), hypovolaemia. Cardiologists performing pharmacologic stress echocardiography are well aware of the risks deriving from administration of dobutamine in patients with any of the conditions listed above; therefore, the MAH believes that, following the lifting of contraindications for SonoVue, the risk of SonoVue-enhanced stress echocardiography with dobutamine in

critically ill patients is not going to increase. In particular, the risk of severe cardiac arrhythmias during stress-echo procedures is not going to increase, as dobutamine is specifically contraindicated for use in patients with predisposition for or documented medical history of clinically significant or chronic arrhythmia.

While contraindications are lifted from Section 4.3, the MAH proposes to introduce a specific warning in Section 4.4. of the SmPC of the product. This would increase prescriber's/user's awareness of the conditions for which stress echocardiography with dobutamine is contraindicated. In addition, the "Checklist For Good Reporting" included in the SonoVue educational material has been expanded in order to include a specific "cardiac form" aimed at recording information on cardiovascular history of the patient, cardiovascular co-morbidities, co-medications, type of echocardiography examination, and echocardiography findings. The aim has been broadened to inform the healthcare professionals of the importance of appropriately assessing the presence and recording data on patients' cardiovascular history, underlying disease(s), co-medications, type of echocardiography procedure, and echocardiography findings. This checklist will also help identifying conditions for which the use of dobutamine is contraindicated.

As for the 5 cases of severe cardiac arrhythmias in the MAH pharmacovigilance database, two (ES-000872 and BR0-010389) were observed in the context of anaphylactic reactions, a known and rare occurrence reported for both SonoVue and dobutamine. Two other cases (GB-000813 and GB-000089) most likely occurred after the onset of a vasovagal reaction, an adverse event that could have been caused by a dynamic functional outflow obstruction resulting from dobutamine inotropic action or by a Bezold-Jarish reflex, due to excessive inotropic stimulation, especially during the early stage of dobutamine infusion. In the last of the 5 cases (GB-000374) there was no evidence for a contrast reaction and the reporter considered the ventricular fibrillation as probably related to the administration of dobutamine.

As previously reported by the MAH, the concomitant use of stressors may represent an important confounding factor in the assessment of cases of serious adverse reactions to SonoVue in echocardiography. Stressors may induce predictable, dose-dependent effects on the cardiovascular system (e.g., increase in heart rate, blood pressure and ventricular ectopic activity for dobutamine, or decrease in blood pressure for adenosine and dipyridamole) as well as unpredictable, hypersensitivity reactions. Of note, it is known that hypersensitivity reactions may follow the administration of the approved pharmacological stressors.

3. Overall conclusion and impact on the benefit/risk balance

SonoVue is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio. SonoVue should only be used in patients where study without contrast enhancement is inconclusive:

- Echocardiography: SonoVue is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation.

- Doppler of macrovasculature: SonoVue increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal to noise ratio. SonoVue increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment.

- *Doppler of microvasculature: SonoVue improves display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.*

The MAH proposed the update of section 4.3 of the SmPC in order to delete the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease and to insert information on these patient populations into section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. The Package Leaflet was proposed to be updated accordingly.

Based on the results of BR1-132 study, post-marketing data and the safety profile of the other UCAs approved in Europe, this variation for SONOVUE for the following proposed changes of 4.3 and 4.4 sections of the SmPC is considered approvable by the CHMP. The MAH has been requested by the CHMP to closely monitor and provide discussion, via the next PSUR, regarding the recorded events with a comparison of the reporting rates specifically on the above defined high risk patient population during the time period when the contra-indication was in effect (2004-today) versus the time period the contra-indication will be removed (today onwards).

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		Type
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of section 4.3 of the SmPC in order to delete the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease and to insert information on these patient populations into section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. The Package Leaflet was proposed to be updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.