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

Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 203684
Drug Name:	**Lumason (**sulfur hexafluoride microspheres for injectable suspension)
Proposed Indication(s):	Lumason is an ultrasound contrast agent indicated for use in adult and pediatric patients, (b) (4) characterization of focal liver lesions
Applicant:	Bracco Diagnostic Inc.
Date(s):	NDA Submission: June 4, 2015 PDUFA Date: April 4, 2016
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Keywords: Sensitivity, Sensitivity, Specificity, Efficacy, Safety, Confidence Interval

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1. EXECUTIVE SUMMARY

The sponsor's interaction with the FDA on this NDA started in 2009. After numerous meetings and exchange of information, two phase III studies were designed and conducted based on guidance given by the FDA Division of Medical Imaging Products (DMIP) to the Sponsor.

The sponsor submitted the results of two identical, independently conducted Phase III clinical studies, BR1-128 and BR1-130, to support the indication. Both studies are titled: "Characterization of Focal Liver Lesions with SonoVue-enhanced Ultrasound Imaging: A Phase III, Intra-patient Comparative Study versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging/Clinical Data as Truth Standard." The primary objective of both BR1-128 and BR1-130 was to demonstrate that the sensitivity and specificity of SonoVue-enhanced ultrasound for the characterization of benign versus malignant focal liver lesions (FLLs) are superior to sensitivity and specificity of unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast-enhanced computed tomography [CE-CT] and/or contrast-enhanced magnetic resonance imaging [CE-MRI])/clinical data as truth standard.

The primary efficacy endpoint of the two studies, i.e., the characterization of lesions as benign (specificity) or malignant (sensitivity), was prospectively defined. The sponsor included FDA's recommendation in these two studies. The analysis population was Intent to Diagnose (ITD) population where all subjects who received SonoVue and enrolled in the efficacy phase (i.e., after the end of the training phase), had a definite final diagnosis (benign or malignant) from the truth standard and had unenhanced and SonoVue-enhanced ultrasonography available. All efficacy analyses were based on data from the ITD population.

The proposed indication is "Lumason is indicated for use in adults and pediatric patients (b) (4) characterization of focal liver lesions."

A total of 499 patients with at least 1 focal liver lesion requiring work-up for characterization were included in two studies, BR1-128 and BR1-130. Study BR1-128 had 240 ITD subjects and the study BR1-130 had 259 ITD subjects. All patients had off-site ultrasound evaluations and a definite final diagnosis from truth standard. Among these patients, there were 259 men and 240 women. The mean age was 56 years (range 19 to 93 years). The racial and ethnic representations were 73.5% Caucasian, 10.8% Black, 9.2% Hispanic, 5.4% Asian, and 1% other racial or ethnic groups. The mean weight was 177.1 lbs. (range 96.8 to 380.6 lbs.).

The Truth standard included: histology/surgery; or contrast-enhanced CT and/or contrast-enhanced MRI and/or 6 month follow-up. For each study, the interpretation of images was conducted by three independent radiologist readers who were blinded to clinical data. Separate blinded readers assessed the truth standard images.

Tables 1 and 2 summarize the diagnostic performance on off-site and on-site ultrasound assessment of primary efficacy by blinded and on-site readers for two studies.

Table 1: Diagnostic Performance in Study BR1-128 (N = 240 ITD population)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
n = 240	124	116	124	116	124	116	124	116
Sensitivity (%) 95% CI	**53.2 (24, 62)**	**64.5 (56, 73)**	**41.1 (33, 50)**	**60.5 (52, 69)**	**66.1 (58, 75)**	**46.8 (38, 56)**	**33.9 (26, 43)**	**87.9 (81, 93)**
Difference	11.3[a]		19.4[b]		-19.3 [b]		55.0 [b]	
CI on Diff	(-1.1, 23.4)		(6.6, 31.6)		(-31.4, -6.9)		(43.1, 63.7)	
Specificity (%) 95% CI	**24.1 (16, 32)**	**71.6 (63, 80)**	**6.9 (2, 12)**	**67.2 (59, 76)**	**58.6 (50, 68)**	**87.9 (82, 94)**	**24.1 (17, 33)**	**90.5 (84, 95)**
Difference	47.5 [b]		60.3 [b]		29.3 [b]		66.4 [b]	
CI on Diff	(35.3, 58.4)		(49.8, 69.6)		(17.9, 40.0)		(56.0, 75.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.0754.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

Table 2: Diagnostic Performance in Study BR1-130 (N = 259 ITD population)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
Parameter - N	119	140	119	140	119	140	119	140
Sensitivity (%) 95% CI	**48.7 (40, 58)**	**86.6 (80, 92)**	**35.3 (27, 44)**	**75.6 (68, 83)**	**16.0 (9, 24)**	**91.6 (87, 97)**	**40.3 (31, 50)**	**90.8 (84, 95)**
Difference	37.9[b]		40.3 [b]		75.6 [b]		50.5 [b]	
CI on Diff	(30.4, 54.2)		(28.6, 51.7)		(66.5, 83.5)		(44.4, 65.4)	
Specificity (%) 95% CI	**62.9 (55, 71)**	**70.7 (63, 78)**	**54.3 (46, 63)**	**82.9 (77, 89)**	**22.1 (15, 23)**	**72.9 (66, 80)**	**19.3 (13, 27)**	**78.6 (71, 85)**
Difference	7.8[a]		28.6 [b]		50.8 [b]		59.3 [b]	
CI on Diff	(-3.8, 21.1)		(20.9, 44.4)		(40.1, 60.6)		(49.1, 68.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.1380.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

The protocol defined success criteria was that the sensitivity and specificity must be statistically superior for the same readers for at least two out of 3 blinded readers in each of the two studies. The protocol defined efficacy criteria were met for the study BR1-130 where the sensitivity and specificity were both statistically superior in the same reader for 2 of the 3 off-site readers analyzing their data separately; but were not met for the study BR1-128. The sensitivity and specificity were both statistically superior in one reader, but the specificity was statistically superior for the reader 3, sensitivity was numerically greater for reader 1. This study did not meet statistically defined success criteria.

For the study BR1-128, reader to reader variability existed. Also, the diagnostic ability of readers for unenhanced ultrasound (UE-US) is no better than random for readers 1 and 2 in study BR1-128 and readers 2 and 3 in BR1-130, i.e., 4 of the 6 blinded readers without contrast is worse than random guessing.

Overall, in the primary analysis of sensitivity (characterization of lesions as malignant), SonoVue enhanced ultrasound increased the sensitivity in 5 of the 6 blinded readers, as compared to unenhanced ultrasound; the increase in sensitivity was statistically significant for 4 of the readers and one reader did not show an increase in sensitivity with SonoVue-enhanced ultrasound.

In the primary analysis of specificity (characterization of lesions as benign), all 6 blinded readers showed an increase in specificity with SonoVue-enhanced ultrasound in comparison with unenhanced ultrasound. Differences in specificity between CE-US and UE-US were statistically significant for 5 of the readers and for the sixth reader, the specificity increased with SonoVue-enhanced ultrasound, but the difference was not statistically significant.

For the secondary endpoints of Accuracy, positive predictive value (PPV) and negative predictive value (NPV), CE-US consistently provided higher values than from UE-US for Accuracy, PPV and NPV for both studies – BR1-128 and BR1-130 (ITD population). The diagnostic performance by gender, race, age and geographical region was similar to those observed in the whole population.

The safety and overall efficacy is favorable to characterization of focal liver lesions with SonoVue-enhanced ultrasound imaging. Approval is recommended for the proposed indication.

2. INTRODUCTION

Lumason™ (sulfur hexafluoride lipid-type A microspheres) is an ultrasound contrast agent developed by Bracco and has a microsphere structure, consisting of a low solubility gas, sulfur hexafluoride (SF_6), stabilized by a phospholipid shell.

^{68}Ga-DOTATATE is a radiopharmaceutical product used for functional imaging with positron emission tomography (PET) when the increased expression of somatostatin receptor (SSTR) is a diagnostic target. Several types of tumors are known to significantly express SSTR and therefore the density of SSTR expression may be visualized with ^{68}Ga-DOTATATE.

2.1 Overview

Lumason(sulfur hexafluoride lipid-type A microspheres) has been approved by the United States Food and Drug Administration (US FDA) for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Lumason has been commercialized under the brand name SonoVue® in Europe since 2001. SonoVue is currently approved for intravenous use in 39 countries throughout the world, outside the United States of America (USA), and is marketed in 26 countries.

SonoVue is not currently approved for use in pediatric patients for any indication in any country

Bracco Diagnostics Inc. submitted this supplemental New Drug Application (sNDA) to the FDA, seeking an additional indication for Lumason as follows:

"Lumason is indicated for use in adults and pediatric patients (b) (4) *the characterization of focal liver lesions."*

2.1.1 Regulatory History

The Sponsor submitted the results of two identical, independently conducted Phase III clinical studies, BR1-128 and BR1-130, to support the indication. Both studies are titled: "Characterization of Focal Liver Lesions with SonoVue-enhanced Ultrasound Imaging: A Phase III, Intra-patient Comparative Study versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging/Clinical Data as Truth Standard."

The two phase III studies were designed and conducted based on guidance given by the FDA Division of Medical Imaging Products (DMIP) to the Sponsor.

The primary efficacy endpoint of the two studies, i.e., the characterization of lesions as benign (specificity) or malignant (sensitivity), was prospectively defined and agreed upon with the FDA. The two study protocols were discussed with the FDA and approval provided on the final and amended protocols.

A brief regulatory history is as follows:

- 14 April 2009: The Agency notified the sponsor that their response to FDA comments on clinical and statistical points in the Study BR1-128 protocol (IND 46,958) was acceptable and BR1-128 may proceed.

- 5 May 2009: Clinical study protocol for Study BR1-128 (IND 46,958) was submitted

- 4 March 2010: Clinical study protocol for Study BR1-130 (IND 46,958) submitted.

- 7 July 2010 Type C Meeting held with FDA held and minutes exchanged

- 24 September 2010: submitted amended protocols or BR1-128 and BR1-130 (IND 46,958)

- 1 June 2012: Submitted Blinded Read Methodology and Statistical Analysis Plan for BR1-128 (IND 46,958)

- 3 August 2012: Submitted Blinded Read Methodology and Statistical Analysis Plan for BR1-130 (IND 46,958)

- 4 March 2013: Submitted response to FDA questions on standard of truth in BR1-128 and BR1-130 (IND 46,958); FDA response to the Sponsor stating that the planned truth standard in BR1-128 and BR1-130 is acceptable (23 April 2013)
- 28 October 2014: Face-to face meeting to discuss and receive feedback on the results of the two completed Phase III studies and the appropriateness of documentation to support a regulatory submission for the use of Lumason in FLL characterization during ultrasonography of liver.The Agency's comments and input were addressed, including the additional analyses requested and submission of site level listings requested relevant to Bioresearch Monitoring Program (BIMO) inspections.

2.1.2 Doses

The dose of SonoVue after reconstitution: 2.4 mL to be administered as an intravenous bolus injection during ultrasonography of the liver for focal liver lesion characterization. A second injection of 2.4 mL could be administered in case of technical failure of the first bolus. The 2.4 mL dose is the recommended dose for the microvasculature indication in all countries where SonoVue is registered and it is the dose most commonly used in published clinical experience in this indication. A maximum of 2 injections of 2.4 mL of SonoVue is allowed.

2.1.3 Identified Studies in the review

Two phases III studies (named BR1-128 and BR1-130) conducted in adults in support of this application were designed and conducted based on guidance given by the FDA Division of Medical Imaging Products to Bracco Diagnostics, Inc. The primary efficacy endpoint of the two studies, i.e., the characterization of lesions as benign (specificity) or malignant (sensitivity), was prospectively

defined and agreed upon with the FDA. The two study protocols were discussed with the FDA and approval provided on the final and amended protocols.

Both studies were multicenter, intrapatient comparator studies in which patients underwent both unenhanced and SonoVue-enhanced ultrasound of a target focal liver lesion requiring further work-up for complete characterization of the lesion as malignant or benign.

Statistical Review has focused on these two studies.

2.1.4 Patient Population

Study population consisted of patients of at least 18 years of age with at least 1 focal liver lesion requiring work-up for characterization. A single target lesion was identified as the target FLL. The target lesion could be: a lesion incidentally detected, a lesion in a patient with chronic hepatitis or liver cirrhosis, or a lesion in a patient with a known history of malignancy.

The patient was to be scheduled for surgical removal or biopsy of the target lesion from 24 hours to 30 days after SonoVue administration or, if tissue biopsy was not indicated nor surgery planned, was scheduled for or had a CE-CT and/or CE-MRI of the target lesion either from 30 days to 48 hours prior to SonoVue administration or from 24 hours to
30 days after administration.

2.1.5 Assessment of Images

- For each technically adequate image, lesion characterization for unenhanced and contrast-enhanced ultrasound, including border definition, lesion shape, lesion vascularity, echogenicity and pattern of enhancement
- A diagnostic conclusion (i.e., benign, malignant or indeterminate) for the target lesion
- A detailed diagnosis for the type of lesion:
  - **Malignant**, the types were hepatocellular carcinoma (HCC), hypo- or hypervascular metastases, cystic metastases or cholangiocarcinoma or other/unable to determine;
  - **Benign**, the types were hemangioma, focal nodular hyperplasia (FNH), focal fatty sparing or change, regenerating nodule, simple cyst, adenoma or abscess or other/unable to determine
- The unit of analysis was the lesion; each subject had a single lesion that was to be characterized.

2.1.6 Truth Standard

The truth standard was based on lesion size (on-site histology/pathology) and/or off-site CT/MRI & follow-up:

For FLL ≤1 cm maximum diameter - histology only accepted

For FLL 1 - 2 cm maximum diameter - CE-CT and CE-MRI showed typical vascular pattern

For FLL ≥ 2 cm maximum diameter - CE-CT or CE-MRI showed typical vascular pattern

For subjects without proof of malignancy - Imaging proof of malignancy any time within 6 months after SonoVue injection to show disease progression; tissue pathology/histology of the target lesion obtained at any time during a 6 month follow-up period

2.1.7 Sample Size

For each study, a total enrollment of 246 subjects was needed in order to provide 222 subjects with a target lesion evaluable for efficacy (111 subjects with a malignant lesion and 111 subjects with a benign lesion in each study). A subject **evaluable** for efficacy was defined as one who underwent all study and follow-up procedures, including evaluations to establish final diagnosis based on truth standard as per protocol requirements. Since a 10% drop-out was foreseen in each study, 246 subjects were to be enrolled to obtain 222 evaluable subjects.

2.1.8 Analysis Population:

Safety Population: All subjects who received SonoVue and enrolled during the training phase or efficacy phase are included in the safety population.

Intent-To-Diagnose [ITD] Population: All subjects who received SonoVue and enrolled in the efficacy phase (i.e., after the end of the training phase), had a definite final diagnosis (benign or malignant) from the truth standard and had unenhanced and SonoVue-enhanced ultrasonography available. All efficacy analyses were based on data from the ITD population and had

Per-Protocol Population: The per-protocol population includes ITD subjects without protocol violations.

Sensitivity Analysis Population: For this population, any missing images were supposed to be imputed as false negative (FN) for the positive truth standard diagnosis or false positive (FP) for the negative truth standard diagnosis. In both studies, no patients with definite final diagnosis (benign or malignant) from truth standard had missing ultrasound images. Therefore, there was no need to impute the missing values. ITD population became the primary analysis population.

For the primary analysis in each study, characterization of the target liver lesions was provided by 3 independent off-site assessors, using a blinded reading methodology. Analysis population & Confirmatory Studies in the Evaluation of Efficacy of SonoVue for Characterization of Focal Liver Lesions are given in Table 3.

Table 3: Studies in the Characterization of Focal Liver Lesions (Sponsor)

Study	Subjects	Patient Population	Study Design Dose	Efficacy Endpoints
BR1-128 Multicenter 14 centers in USA 1 center in Europe Sept 2009-Jul 2013	**Total[a]: 337** Training: 74 Efficacy: 263 Safety: 337 **ITD[b,c]: 240** Malignant: 124 Benign: 116	18 years of age with at least 1 focal liver lesion requiring work-up for characterization. A single target lesion was identified as the target FLL. The target lesion could be: a lesion incidentally detected, a lesion in a patient with chronic hepatitis or liver cirrhosis, or a lesion in a patient with a known history of malignancy. The patient was to be scheduled for surgical removal or biopsy of the target lesion from 24 hours to 30 days after SonoVue administration or, if tissue biopsy was not indicated nor surgery planned, was scheduled for or had a CE-CT and/or CE-MRI of the target lesion either from 30 days to 48 hours prior to SonoVue administration or from 24 hours to 30 days after administration.	Phase III intrapatient study of SonoVue-enhanced versus unenhanced ultrasound in characterization of focal liver lesions using histology or MR/CT as truth standard Maximum of 2 IV bolus injections of 2.4 mL was allowed to assess the dynamic enhancement profile of the target lesion and surrounding parenchyma. The 2nd dose could be administered in case of technical failure of the first bolus (interval of 30 min between doses)	Characterization of lesions as malignant (sensitivity) or benign (specificity) Primary analysis: comparison of the sensitivity and specificity of SonoVue-enhanced versus unenhanced ultrasound, using diagnoses provided by the 3 off-site assessors
BR1-130 Multicenter 14 centers in USA 5 centers in Europe June 2010-Jul 2013	**Total[a]: 340** Training: 67 Efficacy: 273 Safety: 340 **ITD[b]: 259** Malignant: 119 Benign: 140			
TOTAL	**677**			

[a] Number of patients who received SonoVue.
[b] Population used for primary efficacy analyses; defined as patients enrolled during the efficacy phase of the study and who had a definite final diagnosis from truth standard and off-site ultrasound evaluations available.
[a] Malignant or benign as the final diagnosis based on the truth standard.
Data source: Module 5 Section 5.3.5.2 Study Reports of Uncontrolled Studies BR1-128 and BR1-130

2.2 Data Sources

Data and definition files were provided by the sponsor.

The NDA in eCTD and SAS export files of these data are located at:
EDR Location: \\CDSESUB1\evsprod\NDA203684\ #31

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis provided by the sponsor were adequate. The sponsor's response to the information requests regarding the data clarification and analysis was satisfacotory.

3.2 Evaluation of Efficacy

3.2.1 Study Design

The two phases III studies (BR1-128 and BR1-130) conducted in adults in support of this application were multicenter, intrapatient comparator studies in which patients underwent both unenhanced and SonoVue-enhanced ultrasound of a target focal liver lesion requiring further work-up for complete characterization of the lesion as malignant or benign.

Studies BR1-128 and BR1-130 were identically designed studies to assess the sensitivity and specificity of contrast-enhanced ultrasound with SonoVue, administered intravenously as a bolus at the dose of 2.4 mL, in comparison with unenhanced ultrasound. The design is in accordance with the recommendations from the AIUM1 for clinical trials assessing the efficacy of contrast enhanced ultrasound in liver imaging.

No active controls were used in this study, since no ultrasound contrast agents were approved for characterization of FLLs in the USA. In addition, no placebo control was utilized, since contrast-specific ultrasound technology with saline is not a valid imaging procedure.

The blinded reads were conducted according to a prospectively defined methodology at an independent core laboratory ((b) (4)). Blinded off-site reads of images were performed for each study by 3 independent board-certified radiologists. The readers were unaffiliated with any of the investigational sites for the study in which they participated and were blinded to any patient clinical information and results of other diagnostic and imaging procedures. A different set of blinded readers was used in each of the two studies.

The CT/MRI reader for each study was board-certified, was not affiliated with the study centers and was blinded to any clinical information about the subject or to the diagnosis obtained with CE-US.

Patients must be at least 18 years. With an indeterminate Liver Lesion (FLL), they should be:

- Scheduled for surgical removal or biopsy
- Scheduled for CE-CT and/or CE-MRI (alternate)
- Unenhanced target lesion imaged at low MI (<0.4)
- Unenhanced target lesion located and mapped (Couinaud)
- CE-US performed immediately following U-US

- No controls utilized (no approved contrast agent)

3.2.2 Objective

The primary objective of both BR1-128 and BR1-130 was to demonstrate that the sensitivity and specificity of SonoVue-enhanced ultrasound for the characterization of benign versus malignant focal liver lesions (FLLs) are superior to sensitivity and specificity of unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast-enhanced computed tomography [CE-CT] and/or contrast-enhanced magnetic resonance imaging [CE-MRI])/clinical data as truth standard.

The secondary objectives of the studies were:

- to evaluate the accuracy and other performance parameters (positive predictive value [PPV], negative predictive value [NPV]) of SonoVue-enhanced ultrasound for characterization of benign versus malignant FLLs in comparison to unenhanced ultrasound;
- to evaluate the ability of SonoVue-enhanced ultrasound to obtain a specific diagnosis of FLLs in comparison with unenhanced ultrasound;
- to evaluate the inter-reader agreement in ultrasound image assessment (unenhanced and SonoVue-enhanced separately); and
- to provide evidence of the safety and tolerability of intravenously administered SonoVue in subjects with focal liver disease.

3.2.3 Number of Subjects in the Studies

Analysis Populations – The intent-to diagnose (ITD) population was the primary efficacy analysis population and safety population for safety.

There were 337 and 340 subjects enrolled in Study BR1-128 and Study BR1-130 respectively. Each study was to be conducted at approximately 15 investigational sites. Before study initiation at each site, the sonographer/MD for the study in each center was to undergo specific training, including the performance of contrast-enhanced ultrasound examination for characterization of FLLs in up to 4 enrolled patients. It was prospectively defined that patients enrolled in the training phase of the study were to undergo all safety assessments planned in the study and were to be included in the safety population, but would not be included in the ITD efficacy analyses. Likewise, subjects without truth standard, technically inadequate truth standard and indeterminate diagnosis by truth standard will not be included in ITD population. The remaining subjects (240 in Study BR1-128 and 259 in Study BR1-130) were included in the blinded read ITD Analysis.

The number of subjects in each study is given below in Table 4:

Table 4: Number of Patients in the Studies

	Study BR1-128	Study BR1-130
Patients Enrolled (Safety Population)	337	340
Training Patients	74	67
Efficacy Patients	263	273
Without Truth Standard	5	9
Technically Inadequate Truth Standard	1	2
Indeterminate diagnosis by Truth Standard	9	3
Intent to Diagnose (ITD) Population	**240**	**259**
Malignant	124	119
Benign	116	140

3.2.4 Protocol Defined Methods of Analysis

Truth standards - on-site histology/pathology or off-site CT/MRI

Primary Efficacy Endpoints Evaluation - (Intent-to-Diagnose [ITD] population)

- Sensitivity of SonoVue-enhanced ultrasound is superior as compared to unenhanced ultrasound for at least 2 of the 3 off-site assessors analyzing their data separately.
- Specificity of SonoVue-enhanced ultrasound is superior as compared to unenhanced ultrasound for at least 2 of the 3 off-site assessors analyzing their data separately.
- Sensitivity and specificity is both superior in the same reader.
- Additionally, assessment utilizing "paired images" U-US and CE-US together versus U-US alone

Diagnostic Performance of Ultrasound

The diagnostic performance of ultrasound (unenhanced ultrasound, SonoVue-enhanced ultrasound, and paired unenhanced and SonoVue-enhanced ultrasound) was derived based on the ultrasound diagnosis and final diagnosis from the truth standard. The cross tabulation of focal liver lesion diagnosis is given in Table 5 for truth standard versus ultrasonography.

Table 5: Focal Liver Lesion Diagnosis: Truth Standard versus Ultrasonography

Truth Standard	Ultrasonography		
	Benign	**Indeterminate or Technically Inadequate**	**Malignant**
Benign	True Negative (TN)	False Positive (FP)	False Positive (FP)
Malignant	False Negative (FN)	False Negative (FN)	True Positive (TP)

3.2.5 Demographic and Baseline Characteristics

In study BR1-130, the majority of the 337 subjects were male (180, 53.4%) and white (233, 69.1%). The mean age was 56.1 years (range 18 to 88 years), mean weight was 82.55 kg (range 44.40, 147.60 kg) and mean height was 169.4 cm (range 137 to 198 cm). In study BR1-130, the majority of the 340 subjects were male (182, 53.5%) and white (263, 77.4%). The mean age was 57.2 years (range 22 to 93 years), mean weight was 78.70 kg (range 41.80, 173.20 kg) and mean height was 169.5 cm (range 137 to 195 cm).

The demographic and baseline characteristics for all subjects who received study agent in Study BR1-128 and study BR1-130 are provided in Tables 6 and 7 for ITD population.

Table 6: Baseline Characteristics Studies BR1-128 and BR1-130 **(Sponsor)**

	BR1-128		BR1-130	
Characteristic	Safety Population N = 337[a]	ITD Population n = 240[a]	Safety Population N = 340	ITD Population n = 259[a]
Sex, n (%)				
Male	180 (53.4)	123 (51.3)	182 (53.5)	136 (52.5)
Female	157 (46.6)	117 (48.8)	158 (46.5)	123 (47.5)
Age (years)				
Mean (SD)	56.1 (12.4)	55.0 (12.2)	57.2 (13.3)	56.9 (13.4)
Median	56.0	54.0	59.0	59.0
Range (min, max)	(18, 88)	(19, 88)	(22, 93)	(22, 93)
Age group, n (%)				
<18 years	0	0	0	0
≥18 to <65 years	254 (75.4)	190 (79.2)	238 (70.0)	185 (71.4)
≥65 years	83 (24.6)	50 (20.8)	102 (30.0)	74 (28.6)
Race, n (%)				
White	233 (69.1)	161 (67.1)	263 (77.4)	206 (79.5)
Black	45 (13.4)	32 (13.3)	35 (10.3)	22 (8.5)
Asian	17 (5.0)	15 (6.3)	19 (5.6)	12 (4.6)
Other	42 (12.5)	32 (13.3)	23 (6.8)	19 (7.3)
Weight (kg)				
Mean (SD)	82.55 (19.29)	81.16 (18.84)	78.70 (19.03)	79.83 (19.54)
Median	80.00	78.45	76.90	77.10
Range (min, max)	(44.40, 147.60)	(44.40, 147.20)	(41.80, 173.20)	44.40, 173.20)
Height (cm)				
Mean (SD)	169.4 (10.7)	169.1 (10.4)	169.50 (10.1)	169.6 (10.4)
Median	170.0	170.0	170.0	170.0
Range (min, max)	(137, 198)	(142, 198)	(137, 195)	(137, 195)

Table 7: Baseline Characteristics Combined Studies BR1-128 and BR1-130 **(Sponsor)**

Characteristic	ITD Population N = 499[a]
Sex, n (%)	
Male	259 (51.9)
Female	240 (48.1)
Age (yr)	
N	499
Mean (yr) (SD)	56.0 (12.9)
Median (yr)	56.0
Range (yr) (minimum, maximum)	(19, 93)
Age group, n (%)	
≥18 to <65 years	375 (75.2)
≥65 years	124 (24.8)
Race, n (%)	
White	367 (73.5)
Non-white	132 (26.5)
Weight (kg)	
N	495
Mean (kg) (SD)	80.48 (19.20)
Median (kg)	78.00
Range (kg) (minimum, maximum)	(44.40, 173.20)
Height (cm)	
N	494
Mean (cm) (SD)	169.4 (10.4)
Median (cm)	170.00
Range (cm) (minimum, maximum)	(137, 198)

3.3 Results and Conclusions

3.3.1 Primary Efficacy endpoints:

The focus of this review was primary efficacy analysis. Estimates of sensitivity and specificity of unenhanced and SonoVue-enhanced ultrasound are provided together with 95% CIs, and the differences in sensitivity and specificity between unenhanced and SonoVue-enhanced ultrasound were tested using McNemar's 2-sided Chi-square test. The secondary endpoints of accuracy, positive predictive values (PPV), negative predictive values (NPV) supported the conclusion of primary endpoints. In addition, diagnostic performance parameters of paired assessment of unenhanced and SonoVue-enhanced ultrasound were calculated and included in this review.

A total of 499 patients with at least 1 focal liver lesion requiring work-up for characterization was included in two studies, BR1-128 and BR1-130. The analysis population was Intent to Diagnose (ITD). Study BR1-128 had 240 ITD subjects and the study BR1-130 had 259 ITD subjects. All patients had off-site ultrasound evaluations and a definite final diagnosis from truth standard. Among these patients, there were 259 men and 240 women. The mean age was 56 years (range 19 to 93 years). The racial and ethnic representations were 73.5% Caucasian, 10.8% Black, 9.2% Hispanic, 5.4% Asian, and 1% other racial or ethnic groups. The mean weight was 177.1 lbs (range 96.8 to 380.6 lbs).

Subjects in both studies received intravenous bolus injections of 2.4 mL of Lumason (up to 2 injections were allowed, 90.8% patients received 1 injection). The target lesion was located and imaged using predefined liver maps (Couinaud) to ensure that the same lesion was consistently examined as the target lesion on unenhanced and Lumason-enhanced ultrasound (lesion tracking). Prior to Lumason administration, gray scale and Doppler (color or power imaging) ultrasound investigations of the target lesion were performed using commercially available ultrasound equipment and using standard techniques. Lumason-enhanced ultrasound was performed using contrast-specific imaging modes operating at MI $\leq$ 0.4. The probe was positioned to provide optimal visualization over the target lesion and was kept in the same position for at least 180 seconds.

The truth standard included: histology/surgery; or contrast-enhanced CT and/or contrast-enhanced MRI and/or 6 month follow-up.

For each study, the interpretation of images was conducted by three independent radiologist readers who were blinded to clinical data. Separate blinded readers assessed the truth standard images. Results of both studies demonstrated an improvement in characterization of focal liver lesions with Lumason-enhanced ultrasound images compared to unenhanced images, except for one reader's result for sensitivity.

The diagnostic performance of off-site and on-site Ultrasound Assessment for ITD Population in BR1-128 (N = 240) is given in Table 8. The diagnostic performance of off-site and on-site Ultrasound Assessment for ITD Population in BR1-130 (N = 259) is given in Table 9.

Table 8: Diagnostic Performance – Study BR1-128 (N = 240)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
n = 240	124	116	124	116	124	116	124	116
Sensitivity (%) 95% CI	**53.2 (24, 62)**	**64.5 (56, 73)**	**41.1 (33, 50)**	**60.5 (52, 69)**	**66.1 (58, 75)**	**46.8 (38, 56)**	**33.9 (26, 43)**	**87.9 (81, 93)**
Difference	11.3[a]		19.4[b]		-19.3[b]		55.0[b]	
CI on Diff	(-1.1, 23.4)		(6.6, 31.6)		(-31.4, -6.9)		(43.1, 63.7)	
Specificity (%) 95% CI	**24.1 (16, 32)**	**71.6 (63, 80)**	**6.9 (2, 12)**	**67.2 (59, 76)**	**58.6 (50, 68)**	**87.9 (82, 94)**	**24.1 (17, 33)**	**90.5 (84, 95)**
Difference	47.5[b]		60.3[b]		29.3[b]		66.4[b]	
CI on Diff	(35.3, 58.4)		(49.8, 69.6)		(17.9, 40.0)		(56.0, 75.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.0754.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

Table 9: Diagnostic Performance – Study BR1-130 (N = 259)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
Parameter - N	119	140	119	140	119	140	119	140
Sensitivity (%) 95% CI	**48.7 (40, 58)**	**86.6 (80, 92)**	**35.3 (27, 44)**	**75.6 (68, 83)**	**16.0 (9, 24)**	**91.6 (87, 97)**	**40.3 (31, 50)**	**90.8 (84, 95)**
Difference	37.9[b]		40.3[b]		75.6[b]		50.5[b]	
CI on Diff	(30.4, 54.2)		(28.6, 51.7)		(66.5, 83.5)		(44.4, 65.4)	
Specificity (%) 95% CI	**62.9 (55, 71)**	**70.7 (63, 78)**	**54.3 (46, 63)**	**82.9 (77, 89)**	**22.1 (15, 23)**	**72.9 (66, 80)**	**19.3 (13, 27)**	**78.6 (71, 85)**
Difference	7.8[a]		28.6[b]		50.8[b]		59.3[b]	
CI on Diff	(-3.8, 21.1)		(20.9, 44.4)		(40.1, 60.6)		(49.1, 68.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.1380.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

The protocol defined success criteria was that the sensitivity and specificity must be statistically superior for the same readers for at least two out of 3 blinded readers in each of the two studies. The protocol defined efficacy criteria were met for the study BR1-130 where the sensitivity and specificity were both statistically superior in the same reader for 2 of the 3 off-site readers analyzing their data separately; but were not met for the study BR1-128. For the study BR1-128, reader to reader variability existed. Also, the diagnostic ability in 4 of the 6 blinded readers without contrast is worse than random guessing. The sensitivity and specificity were both statistically superior in one reader, but the specificity was statistically superior for the reader 3, sensitivity was numerically greater for reader 1. This study did not meet statistically defined success criteria.

Overall, in the primary analysis of sensitivity (characterization of lesions as malignant), SonoVue enhanced ultrasound increased the sensitivity of 5 of the 6 blinded readers, as compared to unenhanced ultrasound; the increase in sensitivity was statistically significant for 4 of the readers and one reader did not show an increase in sensitivity with SonoVue-enhanced ultrasound.

In the primary analysis of specificity (characterization of lesions as benign), all 6 blinded readers showed an increase in specificity with SonoVue-enhanced ultrasound in comparison with unenhanced ultrasound. Differences in specificity between CE-US and UE-US were statistically significant for 5 of the readers and for the sixth reader, the specificity increased with SonoVue-enhanced ultrasound, but the difference was not statistically significant.

3.3.2 Secondary Endpoints Results: Accuracy, NPV, PPV, Inter-reader Agreement

The Table 10 provides estimates of Accuracy, PPV and NPV by readers for two studies. This shows that CE-US consistently provided higher values than from UE-US for Accuracy, PPV and NPV for both studies – BR1-128 and BR1-130 (ITD population)

Table 10: Accuracy, PPV, and NPV for two studies

	Secondary Endpoints - ITD Population in BR1-128 (n = 240)							
Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US	UE-US	CE-US
n = 240	124	116	124	116	124	116	124	116
Accuracy (%)	39.2	67.9	24.6	63.8	62.5	66.7	29.2	89.2
PPV (%)	42.9	70.8	32.1	66.4	63.1	80.6	32.3	90.8
NPV (%)	32.6	65.4	9.9	61.4	61.8	60.7	25.5	87.5
	Secondary Endpoints - ITD Population in BR1-130 (n = 259)							
Accuracy (%)	56.4	78.0	45.6	79.5	19.3	81.5	29.0	84.2
PPV (%)	52.7	71.5	39.6	78.9	14.8	74.1	29.8	78.3
NPV (%)	59.1	86.1	49.7	80.0	23.7	91.1	27.6	90.9

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose; PPV, positive predictive value; NPV, negative predictive value;

3.3.3 Inter-reader Agreement:

Inter-reader agreement among the 3 off-site readers in diagnosing target lesions is presented in Table 11. For study BR1-128 the percentage for all 3 readers being in agreement on the diagnosis was 51.7% for CE-US, much higher than UE-US (32.1%). The percentage agreement for 2 of the 3 readers in agreement on the lesion diagnosis was 97.1% for UE-US and 91.7% for CE-US, respectively. For study BR1-130the percentage for all 3 readers being in agreement on the diagnosis was 66.0% for CE-US, much higher than UE-US (28.2%). The percentage agreement for 2 of the 3 readers in agreement on the lesion diagnosis was 94.6% for UE-US and 99.6% for CE-US, respectively.

Table 11: Inter-reader Agreement- Studies BR1-128 and BR-130

Characteristics	BR1-128		BR1-130	
	UE-US N=240	CE-US N=240	UE-US N=259	CE-US N=259
% Agreement: All 3 Off-site readers agree	32.1	51.7	28.2	66.0
% Agreement: 2 out of 3 Off-site readers agree	97.1	91.7	94.6	99.6

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to diagnose
Agreement in the diagnosis of 'Benign'/'Malignant'/'Indeterminate'/'Technically Inadequate'.

3.3.4 Unpaired and Paired Reads

Table 12 provides diagnostic performance of off-site US assessments for unpaired and paired reads – ITD Population. The sensitivity and specificity from both CE and UE+CE reads are similar.

Table 12: Unpaired and Paired Reads – ITD Population

	Study BR1-128 - ITD Population (n= 240)								
	Off-site Reader #1			**Off-site Reader #2**			**Off-site Reader #3**		
	UE	**CE**	**UE+CE**	**UE**	**CE**	**UE+CE**	**UE**	**CE**	**UE+CE**
Sensitivity (%) 95% CI	53% (44,62)	65% (56,73)	57% (48,65)	41% (33,50)	61% (52,69)	64% (55,72)	66% (58,75)	47% (38,56)	56% (47,64)
Specificity (%) 95% CI	24% (16,32)	72% (63,80)	77% (69,84)	7% (2,12)	67% (59,76)	79% (72,87)	59% (50,68)	88% (82,94)	89% (83,95)
	Study BR1-130 - ITD Population (n= 259)								
	Off-site Reader #1			**Off-site Reader #2**			**Off-site Reader #3**		
	UE	**CE**	**UE+CE**	**UE**	**CE**	**UE+CE**	**UE**	**CE**	**UE+CE**
Sensitivity (%) 95% CI	49% (40,58)	87% (80,92)	79% (73,86)	35% (27,44)	76% (68,83)	82% (76,89)	16% (9,23)	92% (87,97)	92% (87,97)
Specificity (%) 95% CI	62% (55,71)	71% (63,78)	79% (73,86)	54% (46,63)	83% (77,89)	86% (80,92)	22% (15,23)	73% (66,80)	76% (69,83)

3.3.4 Pediatric Subjects:

There are no Bracco-sponsored studies in the pediatric population. The sponsor included available information about intravenous use of Lumason in the pediatric population, with specific reference to liver lesion characterization, in this NDA based on literature search using applicable guidelines and eligibility criteria.

Among the 50 unique references identified during the literature searches, 12 reported on the use of SonoVue in a population <18 years of age; this included 8 papers in which SonoVue was administered intravenously, 3 papers in which a route of administration other than IV was used, and 1 paper in which IV and intravesicle administration of SonoVue were reported. A total of 6 references met all selection criteria. Of these 6 publications, one publication, Jacob et al reported efficacy of SonoVue in the characterization of FLLs in the pediatric population; safety information is also presented in the paper.

This was a prospective study and conducted to evaluate the diagnostic performance of Lumason enhanced ultrasound in the characterization of grey-scale sonographic indeterminate FLLs in pediatric practice. Forty-four children (21 female, 23 male; median age 11.5yrs; range 4 – 18yrs) were included in the study. In this published study, 44 patients with an indeterminate focal liver lesion (23 males, 21 females, age range: 4-18 years, median 11.5 years) were evaluated after intravenous bolus administration of 1.2-2.4 mL of Lumason. Objective was to correlate the findings of CEUS with the findings on CT, MRI or histology. Specificity was 98% (43/44).

3.4 Evaluation of Safety

There were 6,984 healthy volunteers and patients in the safety database. The number of patients with at least one adverse event (AE) related to SonaVue was 569 (5.3%), mostly mild or moderate AEs. There were 2 (< 0.1 %) severe AEs reported and no deaths reported. There are no safety concerns.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Diagnostic Performance by Gender

The diagnostic performance **of** off-site ultrasound assessment for ITD population by Gender is given in Table 13. In both studies, trends for both gender subgroups are similar to those observed in the whole population

Table 13: Diagnostic Performance by Gender

	Reader 1		Reader 2		Reader 3	
	UE	CE	UE	CE	UE	CE
	Study BR1-128 – Female subjects (n=117)					
Sensitivity (n=35)	54.3	74.3	40.0	68.6	65.7	62.9
Specificity (n=82)	24.4	73.2	4.9	68.3	59.8	90.2
	Study BR1-128 – Male subjects (n=123)					
Sensitivity (n=89)	52.8	60.7	41.6	57.3	66.3	40.4
Specificity (n=34)	23.5	67.6	11.8	64.7	55.9	82.4
	Study BR1-130 – Female subjects (n=123)					
Sensitivity (n=34)	44.1	82.4	38.2	76.5	23.5	91.2
Specificity (n=89)	61.8	73.0	51.7	84.3	16.9	69.7
	Study BR1-130 - Male subjects (n=136)					
Sensitivity (n=85)	50.6	88.2	34.1	75.3	12.9	91.8
Specificity (n=51)	64.7	66.7	58.8	80.4	31.4	78.4

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
The unit of analysis was the lesion; each subject had a single lesion that was to be characterized
Sensitivity and Specificity are in percent (%) and n is the denominator for percentage calculation

4.1.2 Diagnostic Performance by Race

The diagnostic performance **of** off-site ultrasound assessment for ITD population by race is given in Table 14. There were smaller number of patients in the non-white race subgroup in both studies, since patients of white race were in the great majority of the total population. In both studies, trends for the white race subgroup are similar to those observed in the whole population

Table 14: Diagnostic Performance by Race

	Reader 1		Reader 2		Reader 3	
	UE	CE	UE	CE	UE	CE
	Study BR1-128 – White subjects (n=161)					
Sensitivity (n=73)	53.4	71.2	45.2	65.8	67.1	54.4
Specificity (n=88)	23.9	71.6	6.8	67.0	62.5	87.5
	Study BR1-128 – Non-white subjects (n=79)					
Sensitivity (n=51)	52.9	54.0	35.3	52.9	64.7	37.3
Specificity (n=28)	25.0	71.4	7.1	67.9	46.4	89.3
	Study BR1-130 – White subjects (n=206)					
Sensitivity (n=90)	46.7	85.6	36.7	77.8	14.4	91.1
Specificity (n=116)	64.7	69.0	53.4	81.0	24.1	68.1
	Study BR1-130 - Non-white subjects (n=53)					
Sensitivity (n=29)	55.2	89.7	31.0	69.0	20.7	93.1
Specificity (n=24)	54.2	79.2	58.3	91.7	12.5	95.8

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
The unit of analysis was the lesion; each subject had a single lesion that was to be characterized
Sensitivity and Specificity are in percent (%) and n is the denominator for percentage calculation

4.1.3 Diagnostic Performance by Age Group

The diagnostic performance **of o**ff-site ultrasound assessment for ITD population by age group is given in Table 15. There were smaller number of patients in the ≥65 years age group, since those <65 years of age were the great majority of the total population. For patients in the age group between 18 and 64 years (N = 190), trends are similar to those observed in the whole population. Variability among readers was observed in both age group and studies. However, overall differences in effectiveness were not observed between younger and ≥ 65 years old subjects. The results are given in the following Table 15.

Table 15: Diagnostic Performance by Age Group

	Reader 1		Reader 2		Reader 3	
	UE	CE	UE	CE	UE	CE
	Study BR1-128 - Age 18-64 (n=190)					
Sensitivity (n=122)	52.8	57.3	39.3	57.3	69.7	41.6
Specificity (n=103)	22.8	70.3	5.9	69.3	59.4	88.1
	Study BR1-128 - Age ≥ 65 (n=50)					
Sensitivity (n=2)	54.3	82.9	45.7	68.6	57.1	60.0
Specificity (n=13)	33.3	80.0	13.3	53.3	53.3	86.7
	Study BR1-130 - Age 18-64 (n=185)					
Sensitivity (n=81)	54.3	92.9	34.3	74.3	15.7	91.4
Specificity (n=85)	64.3	75.7	50.4	86.1	23.5	76.5
	Study BR1-130 - Age ≥ 65 (n=74)					
Sensitivity (n=70)	40.8	91.8	36.7	77.6	16.3	91.8
Specificity (n=115)	56.0	48.0	72.0	68.0	16.0	56.0

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
The unit of analysis was the lesion; each subject had a single lesion that was to be characterized
Sensitivity and Specificity are in percent (%) and n is the denominator for percentage calculation

4.1.4 Diagnostic Performance by Geographical Region

In the study BR1-128 there were 14 centers form North America (US & Canada) and 1 European center with the number of patients ranging from 3 (1.3%) to 37 (15.4%) out of total 240 patients The time framework of the studies in BE1-128 was from Sept 2009 to July 2013. In the study BR1-130 there were 14 centers form North America (US & Canada) and 5 European Centers with the number of patients ranging from 1 (0.4%) to 33 (12.7%) out of total 259 patients The time framework of the studies in BR1-130 was June from 2010 to July 2013. The review team decided to focus on two geographical regions (North America & Europe)

The diagnostic performance by geographical region (North America & Europe) is given in Table 16. There was smaller number of patients in the Europe subgroup in both studies. Patients of North America subgroup were in the great majority of the total population. In both studies, trends for the both regions are similar to those observed in the whole population

Table 16: Diagnostic Performance by Geographical Region

	Study BRI-128							
	Reader 1		Reader 2		Reader 3		On-site	
	UE	CE	UE	CE	UE	CE	UE	CE
	Study BR1-128 - North America							
Sensitivity (n=122)	52.5	64.8	41.0	59.8	65.6	47.5	33.6	87.7
Specificity (n=103)	25.2	68.0	6.8	65.0	29.2	86.4	26.2	89.3
	Study BR1-128 - Europe							
Sensitivity (n=2)	100.0	50.0	50.0	100.0	100.0	0.0	50.0	100.0
Specificity (n=13)	15.4	100.0	7.7	84.6	53.8	100.0	7.7	100.0
	Study BRI-130 - North America							
Sensitivity (n=81)	50.6	92.6	30.9	80.2	17.3	92.6	44.4	92.6
Specificity (n=85)	64.7	68.2	54.1	83.5	18.8	75.3	18.8	70.6
	Study BR1-130 - Europe							
Sensitivity (n=38)	44.7	73.7	44.7	65.8	13.2	89.5	31.6	86.8
Specificity (n=55)	60.0	74.5	54.5	81.8	27.3	69.1	20.0	90.9

North America includes USA and Canada
UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
The unit of analysis was the lesion; each subject had a single lesion that was to be characterized
Sensitivity and Specificity are in percent (%) and n is the denominator for percentage calculation

4.2 Other Special/Subgroup Populations

The lesion size was identified as a special subgroup of interest by the clinical team. The diagnostic performance by lesion size (≤ 2 cm, > 2 cm to ≤ 4 cm, Lesion Size > 4 cm) is given in Table 17. There was smaller number of patients in ≤ 2 cm in both studies. In both studies, trends all lesion size group are similar to those observed in the whole population

Table 17: Diagnostic Performance by Lesion Size

	Study BRI-128							
	Reader 1		Reader 2		Reader 3		On-site	
	UE	CE	UE	CE	UE	CE	UE	CE
	Study BR1-128 – Lesion Size ≤ 2 cm							
Sensitivity (n=16)	25.0	56.3	25.0	37.5	68.8	50.0	12.5	75.0
Specificity (n=32)	25.0	71.9	3.1	62.5	59.4	81.3	34.4	90.6
	Study BR1-128 - Lesion Size > 2 cm to ≤ 4 cm							
Sensitivity (n=62)	54.8	62.9	38.7	62.9	61.3	48.4	35.5	85.5
Specificity (n=57)	24.6	73.7	7.0	68.4	63.2	89.5	17.5	89.5
	Study BR1-128 - Lesion Size > 4 cm							
Sensitivity (n=46)	60.9	69.6	50.0	65.2	71.5	43.5	39.1	97.7
Specificity (n=27)	22.2	66.7	11.1	70.4	48.1	92.6	25.9	92.6
	Study BR1-130 - – Lesion Size ≤ 2 cm							
Sensitivity (n=16)	31.3	81.3	6.3	56.3	0.0	81.3	18.8	81.3
Specificity (n=30)	66.7	76.7	70.0	90.0	30.0	56.7	30.0	73.3
	Study BR1-130 - Lesion Size > 2 cm to ≤ 4 cm							
Sensitivity (n=50)	46.0	88.0	38.0	86.0	14.0	90.0	42.0	94.0
Specificity (n=62)	67.7	67.7	61.3	87.1	30.6	82.3	17.7	77.4
	Study BR1-130 - Lesion Size > 4 cm							
Sensitivity (n=53)	56.6	86.8	41.5	71.7	22.6	96.2	45.3	90.6
Specificity (n=48)	54.2	70.8	35.4	72.9	6.3	70.8	14.6	83.3

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
The unit of analysis was the lesion; each subject had a single lesion that was to be characterized
Sensitivity and Specificity are in percent (%) and n is the denominator for percentage calculation

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor's interaction with the FDA on this NDA started in 2009. After numerous meetings and exchange of information, two phase III studies were designed and conducted based on guidance given by the FDA Division of Medical Imaging Products (DMIP) to the Sponsor.

The sponsor submitted the results of two identical, independently conducted Phase III clinical studies, BR1-128 and BR1-130, to support the indication. Both studies are titled: "Characterization of Focal Liver Lesions with SonoVue-enhanced Ultrasound Imaging: A Phase III, Intra-patient Comparative Study versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging/Clinical Data as Truth Standard." The primary objective of both BR1-128 and BR1-130 was to demonstrate that the sensitivity and specificity of SonoVue-enhanced ultrasound for the characterization of benign versus malignant focal liver lesions (FLLs) are superior to sensitivity and specificity of unenhanced ultrasound, using final diagnosis based on histology or combined imaging (contrast-enhanced computed tomography [CE-CT] and/or contrast-enhanced magnetic resonance imaging [CE-MRI])/clinical data as truth standard.

The primary efficacy endpoint of the two studies, i.e., the characterization of lesions as benign (specificity) or malignant (sensitivity), was prospectively defined and agreed upon with the FDA. The two study protocols were discussed with the FDA and approval provided on the final and amended protocols. The analysis population was Intent to Diagnose (ITD) population where all subjects who received SonoVue and enrolled in the efficacy phase (i.e., after the end of the training phase), had a definite final diagnosis (benign or malignant) from the truth standard and had unenhanced and SonoVue-enhanced ultrasonography available. All efficacy analyses were based on data from the ITD population.

The proposed indication is "Lumason is indicated for use in adults and pediatric patients (b) (4) characterization of focal liver lesions."

A total of 499 patients with at least 1 focal liver lesion requiring work-up for characterization were included in two studies, BR1-128 and BR1-130. Study BR1-128 had 240 ITD subjects and the study BR1-130 had 259 ITD subjects. All patients had off-site ultrasound evaluations and a definite final diagnosis from truth standard. Among these patients, there were 259 men and 240 women. The mean age was 56 years (range 19 to 93 years). The racial and ethnic representations were 73.5% Caucasian, 10.8% Black, 9.2% Hispanic, 5.4% Asian, and 1% other racial or ethnic groups. The mean weight was 177.1 lbs. (range 96.8 to 380.6 lbs.).

The truth standard included: histology/surgery; or contrast-enhanced CT and/or contrast-enhanced MRI and/or 6 month follow-up. For each study, the interpretation of images was conducted by three independent radiologist readers who were blinded to clinical data. Separate blinded readers assessed the truth standard images.

Tables 18 and 19 summarize the diagnostic performance on off-site and on-site ultrasound assessment of primary efficacy by blinded and on-site readers for two studies.

Table 18: Diagnostic Performance in Study BR1-128 (N = 240 ITD population)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
n = 240	124	116	124	116	124	116	124	116
Sensitivity (%) 95% CI	**53.2 (24, 62)**	**64.5 (56, 73)**	**41.1 (33, 50)**	**60.5 (52, 69)**	**66.1 (58, 75)**	**46.8 (38, 56)**	**33.9 (26, 43)**	**87.9 (81, 93)**
Difference	11.3[a]		19.4[b]		-19.3[b]		55.0[b]	
CI on Diff	(-1.1, 23.4)		(6.6, 31.6)		(-31.4, -6.9)		(43.1, 63.7)	
Specificity (%) 95% CI	**24.1 (16, 32)**	**71.6 (63, 80)**	**6.9 (2, 12)**	**67.2 (59, 76)**	**58.6 (50, 68)**	**87.9 (82, 94)**	**24.1 (17, 33)**	**90.5 (84, 95)**
Difference	47.5[b]		60.3[b]		29.3[b]		66.4[b]	
CI on Diff	(35.3, 58.4)		(49.8, 69.6)		(17.9, 40.0)		(56.0, 75.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.0754.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

Table 19: Diagnostic Performance in Study BR1-130 (N = 259 ITD population)

Readers	Off-site Reader 1		Off-site Reader 2		Off-site Reader 3		On-site Reader	
Contrast	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**	**UE-US**	**CE-US**
Parameter - N	119	140	119	140	119	140	119	140
Sensitivity (%) 95% CI	**48.7 (40, 58)**	**86.6 (80, 92)**	**35.3 (27, 44)**	**75.6 (68, 83)**	**16.0 (9, 24)**	**91.6 (87, 97)**	**40.3 (31, 50)**	**90.8 (84, 95)**
Difference	37.9[b]		40.3[b]		75.6[b]		50.5[b]	
CI on Diff	(30.4, 54.2)		(28.6, 51.7)		(66.5, 83.5)		(44.4, 65.4)	
Specificity (%) 95% CI	**62.9 (55, 71)**	**70.7 (63, 78)**	**54.3 (46, 63)**	**82.9 (77, 89)**	**22.1 (15, 23)**	**72.9 (66, 80)**	**19.3 (13, 27)**	**78.6 (71, 85)**
Difference	7.8[a]		28.6[b]		50.8[b]		59.3[b]	
CI on Diff	(-3.8, 21.1)		(20.9, 44.4)		(40.1, 60.6)		(49.1, 68.3)	

UE-US, unenhanced ultrasound; CE-US, contrast-enhanced ultrasound; ITD, intent-to-diagnose
[a] Based on McNemar's test of difference between CE-US and UE-US, p=0.1380.
[b] Statistically significant difference from UE-US (p<0.05 based on McNemar's test).

The protocol defined success criteria was that the sensitivity and specificity must be statistically superior for the same readers for at least two out of 3 blinded readers in each of the two studies. The protocol defined efficacy criteria were met for the study BR1-130 where the sensitivity and specificity were both statistically superior in the same reader for 2 of the 3 off-site readers analyzing their data separately; but were not met for the study BR1-128. The sensitivity and specificity were both statistically superior in one reader, but the specificity was statistically superior for the reader 3, sensitivity was numerically greater for reader 1. This study did not meet statistically defined success criteria.

For the study BR1-128, reader to reader variability existed. Also, the diagnostic ability of readers for unenhanced ultrasound (UE-US) is no better than random for readers 1 and 2 in study BR1-128 and readers 2 and 3 in BR1-130, i.e., 4 of the 6 blinded readers without contrast is worse than random guessing.

Overall, in the primary analysis of sensitivity (characterization of lesions as malignant), SonoVue enhanced ultrasound increased the sensitivity in 5 of the 6 blinded readers, as compared to unenhanced ultrasound; the increase in sensitivity was statistically significant for 4 of the readers and one reader did not show an increase in sensitivity with SonoVue-enhanced ultrasound.

In the primary analysis of specificity (characterization of lesions as benign), all 6 blinded readers showed an increase in specificity with SonoVue-enhanced ultrasound in comparison with unenhanced ultrasound. Differences in specificity between CE-US and UE-US were statistically significant for 5 of the readers and for the sixth reader, the specificity increased with SonoVue-enhanced ultrasound, but the difference was not statistically significant.

For the secondary endpoints of Accuracy, positive predictive value (PPV) and negative predictive value (NPV), CE-US consistently provided higher values than from UE-US for Accuracy, PPV and NPV for both studies – BR1-128 and BR1-130 (ITD population). The diagnostic performance by gender, race, age and geographical region was similar to those observed in the whole population.

5.2 Conclusions and Recommendations

The safety and overall efficacy is favorable to characterization of focal liver lesions with SonoVue-enhanced ultrasound imaging. Approval is recommended for the proposed indication.

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