CONFIDENTIAL

1 Title Page

Quantitative Evaluation of SonoVue®-Enhanced Ultrasonography for Early Identification of Subjects with Hepatocellular Carcinoma Refractory to Sorafenib Therapy: A Phase II Explorative, Intra-Patient Comparative Study versus Contrast-Enhanced MDCT/MRI Imaging

Name of Test Agent:	SonoVue® (sulfur hexafluoride microbubbles)
Protocol No.:	BR1-129
Developmental Phase of Study:	II
Study Initiation Date (first subject enrolled):	16 December 2009
Study Completion Date (last subject completed):	10 September 2010
Study Terminated:	15 September 2010
Off-site Assessment:	22 April 2011
Clinical Trial Report Date:	Final 13 September 2011

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The study described in this report was performed in compliance with Good Clinical Practice (GCP).

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Title of Study: Quantitative Evaluation of SonoVue-Enhanced Ultrasonography for Early Identification of Subjects with Hepatocellular Carcinoma Refractory to Sorafenib Therapy: A Phase II Explorative, Intra-Patient Comparative Study versus Contrast-Enhanced MDCT/MRI Imaging (Protocol BR1-129)

Investigators/Study Centers: This study was conducted in 14 investigational sites throughout Italy. The following investigators enrolled and dosed study participants:

[redacted]

Publication (reference, if any): None

Study Period:	**Phase of Development:** II
First subject enrolled: 16 December 2009	
Last subject completed: 10 September 2010	
Study Terminated: 15 September 2010	
Off-site assessment: 22 April 2011	

Objectives: The primary objective of this study was to assess whether perfusion changes in one target hepatocellular carcinoma (HCC) lesion assessed quantitatively by contrast-enhanced ultrasonography at Week 2 and Week 4 of sorafenib therapy could predict progression of disease at Week 8 assessed by contrast-enhanced multidetector computed tomography or magnetic resonance imaging (CE-MDCT/MRI), using standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

The secondary objectives were:

- To determine whether perfusion changes in one target HCC lesion assessed quantitatively by contrast-enhanced ultrasonography at Week 2 and Week 4 of sorafenib therapy could:
  - predict progression of disease at Week 8 assessed by CE-MDCT/MRI, using modified response criteria proposed by Llovet et al;
  - correlate with overall survival (OS);
  - correlate with time to progression (TTP) according to RECIST and Llovet et all criteria; or
  - predict progression of the same lesion at Week 8 assessed by Llovet et al criteria.
- In subjects classified as responders at Week 8, to determine whether perfusion changes in the target HCC lesion assessed quantitatively by contrast-enhanced ultrasonography at greater than 8 weeks could identify earlier than CE-MDCT/MRI, HCC progression after Week 8.
- To assess whether progression of the target HCC lesion determined by the Investigator based on qualitative evaluation of contrast-enhanced ultrasonography findings at Week 2 and Week 4 of sorafenib therapy predicted progression of disease at Week 8 assessed by CE-MDCT/MRI, using standard RECIST criteria.
- To compare the diagnostic performance of qualitative evaluation of contrast-enhanced ultrasonography at Week 2 and Week 4 of sorafenib therapy versus the best quantitative parameter enabling prediction of primary resistance to sorafenib.
- To assess the safety and tolerability of SonoVue-enhanced ultrasonography in the target population.

Due to the early termination of the study, formal analyses were not performed for any of the efficacy objectives. All data were presented in the data listings.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Study Design: This was a Phase II explorative multicenter study with intra-patient comparison of SonoVue-enhanced ultrasonography of the liver versus CE-MDCT/MRI in monitoring response to sorafenib therapy in subjects with advanced HCC. The study was primarily designed to explore the feasibility of early identification of HCC subjects refractory to sorafenib therapy based on vascular changes in one target liver lesion quantitatively assessed by contrast-enhanced ultrasonography. The aim was to select the best quantitative parameter(s), the relevant threshold value, and the best timing enabling prediction of primary resistance to study medication in the target population. Study visits are referred to as Week X (Visit X) and correspond as follows:

Visit	**Treatment Phase**	**Scheduled Time**
Within 4 weeks (Visit -4)	Pre-treatment	Within 4 weeks prior to start of sorafenib treatment
Within 1 week (Visit 1)	Pre-treatment	Within 1 week prior to start of sorafenib treatment (baseline)
Week 2 (Visit 2)	On treatment	2 weeks after the start of sorafenib treatment
Week 4 (Visit 3)	On treatment	4 weeks after the start of sorafenib treatment
Week 8 (Visit 4)	On treatment	8 weeks after the start of sorafenib treatment
Week 16 (Visit 5)	On treatment	16 weeks after the start of sorafenib treatment
Week 24 (Visit 6)	On treatment	24 weeks after the start of sorafenib treatment
Week 32 (Visit 7)	On treatment	32 weeks after the start of sorafenib treatment

Follow-up visits (> Week 32 up to 2 years [Visit 8]) were anticipated for any subjects alive at Week 32 (Visit 7) at 3-month intervals for survival up to 2 years after their entry into the study. However, due to the early termination of this study, no information has been collected for any subject beyond Week 32 (Visit 7).

Subject Population: The target population was defined as subjects with advanced HCC who were candidates to receive sorafenib monotherapy, and who had at least one target lesion evaluable by contrast-enhanced ultrasonography which was measurable by RECIST criteria. Of the 168 subjects planned to be included in this study (134 evaluable for the primary end-point), 30 were enrolled, administered at least one dose of SonoVue and evaluated for safety. Twenty-one subjects had data through Week 8 (Visit 4) and 1 subject had visits through Week 32 (Visit 7). This study was terminated early due to slow enrolment of subjects into the trial.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible to participate in this study if they were at least 18 years of age, provided informed consent, were willing to comply with protocol requirements, met the definition of the target population, and were at least 4 weeks post surgery or treatment with resolution of all acute toxic effects. Subjects were considered to be ineligible for inclusion if they had: any clinically unstable cardiac condition prior to SonoVue administration (i.e., evolving or ongoing myocardial infarction, history of acute myocardial infarction or percutaneous coronary intervention within 3 months prior to this study, worsening of typical angina at rest or significant worsening of cardiac symptoms within 7 days prior to this study, recent coronary artery intervention or other factors suggesting clinical instability, cardiac failure Class III/IV according to New York Heart Association, or severe cardiac rhythm disorders); respiratory failure or known history of pulmonary hypertension; known allergy to one or more of the ingredients of the investigational product or the contrast agents used during MDCT and/or MRI; had any other contraindication to one of the imaging examinations (ultrasound, MDCT or MRI), e.g., implants, claustrophobia, inadequate medical conditions, etc.; or any contraindication to sorafenib. Subjects who received an investigational compound within 30 days prior to admission of this study, had a medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data or completing the study and/or postdose follow-up visits, were clinically unsuitable per the Investigator or were pregnant/lactating women were also excluded.

Dose and Mode of Administration, Batch Number of Test Agent: SonoVue was to be administered intravenously into an upper extremity vein as 2.4 mL bolus injection in approximately 2 seconds using a 20-gauge catheter in aseptic conditions. A maximum of 2 injections of 2.4 mL of SonoVue (for a total of 4.8 mL) was to be administered at each evaluation time. The first injection of SonoVue was to be used to assess the dynamic enhancement profile of the contrast agent within the target lesion and the surrounding parenchyma. The second injection was to be performed in case of technical failure of the first bolus and only after the complete disappearance of SonoVue from sinusoidal circulation of the liver. The batch number was [redacted]

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Duration of Treatment: The ultrasound examination was to be completed within 90 minutes. Safety monitoring was to begin at the time of signed informed consent and continued for 30 minutes after the administration of SonoVue. The overall study duration was to be 33 months; however, the study was terminated early due to slow enrolment, therefore, the majority of subjects were only followed up until Week 8 (Visit 4), with few subjects followed to Week 32 (Visit 7).

Evaluation Parameters:

Prior to the examinations, the following data were to be recorded for each subject:

- Demographic data;
- Medical history and physical examination;
- Details of contrast-enhanced MDCT or MRI and chest X-ray;
- Other tumor imaging;
- RECIST assessments;
- Vital signs;
- Concomitant medications; and
- Adverse events.

Ultrasound: Identification and Documentation of Target HCC Lesion at Baseline – At baseline, the Investigator was to identify one HCC lesion evaluable by contrast-enhanced ultrasonography as the contrast-enhanced ultrasonography HCC target lesion. If multiple lesions met the criteria for evaluability by ultrasound, the best evaluable one was to be selected as the target for follow-up considering both the lesion location and the extent of perfusion. To qualify as evaluable by contrast-enhanced ultrasonography, a tumor lesion must have fulfilled the following requirements:

- Acoustic window sufficient for adequate ultrasound examination of the liver (all target HCC borders should have been correctly visualized by B-mode and lesions adjacent to diaphragmatic border should have been avoided);
- Diameter of 2 cm or more;
- Not previously treated;
- Perfused area ≥50% of the total area.

The target HCC lesion was to be located and identified using Coineaud's system and reported on the liver maps included in the case report form (CRF). The maps were to be used to make sure the same HCC was consistently examined as the target lesion at baseline and postdose (lesion tracking). To ensure the same plane of the HCC lesion was evaluated over time, the following parameters were to be measured in B-mode at each evaluation:

- maximum HCC lesion diameters (in millimeters);
- lesion depth (the distance from the transducer to the nearest edge of lesion);
- distance of the lesion from surrounding structures (hepatic vein, hepatic portal vein, common hepatic duct, gallbladder, etc).

The shape of the HCC target lesion was to also be evaluated in B-mode and reported as:

- round,
- elliptical,
- lobular,
- irregular, or
- indeterminate.

These parameters were to be collected and recorded on the CRF at each evaluation.

Contrast enhancement in the target HCC at baseline was to be used as reference for the qualitative evaluation of response by contrast-enhanced ultrasonography during treatment.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Evaluation Parameters (continued):

Ultrasound: Qualitative Evaluation of Response of the Target HCC Lesion – At baseline and at each follow-up visit, the Investigator was to provide his/her evaluation of the extent of vascularization of the target HCC lesion using the following scale: 100% to 75% perfused; 74% to 50% perfused; 49% to 25% perfused; 24% to 0% perfused. At baseline, if the perfusion area of the HCC lesion was <50%, the subject was considered to be ineligible.

At subsequent visits, the Investigator was to reassess the lesion perfusion as described above and was to provide a qualitative evaluation of perfusion changes taking as reference the lowest perfusion observed since the start of treatment. Perfusion changes were to be classified as follows:

Enhancement increased:
- slight increase
- moderate increase
- marked increase

Enhancement stable

Enhancement reduced:
- slight reduction
- moderate reduction
- marked reduction
- no enhancement

The Investigator at each visit was to also indicate whether or not, based on the qualitative assessment, the lesion was progressing.

Ultrasound: Quantitative Evaluation of the Target HCC Lesion – Digital recordings of the ultrasound examinations were to be blinded and quantitatively assessed off-site by an expert reader who was unaffiliated with the study sites and blinded to the medical history of each subject, as well as to the diagnosis obtained by CE-MDCT or MRI/chest X-ray images.

The quantitative analysis of the contrast-enhanced ultrasonography findings at each visit was to be performed using a dedicated quantification software developed by Bracco Research (SonoTumor™ software, version 4.1.2). This tool is able to linearize log-compressed video data from different ultrasound systems providing estimates of perfusion parameters as accurate as from Linear data. It contains an automatic registration algorithm for movement correction and is able to calculate several perfusion parameters (see figure below), namely:

Parameters related to blood volume:
- area under the curve (*Area Under the Curve to infinite time* – AUC)
- perfusion index (*Area Under the Curve / Mean Transit Time*)
- maximum intensity (*Peak of the time-intensity curve* – IMAX)

Parameters related to perfusion dynamic:
- mean transit time (*Time period corresponding to the center of gravity of the perfusion model* – mTT)
- wash-in rate (*Maximum slope in the wash-in phase*)
- rise time (*Time period from the intersection of the maximum slope in the wash-in phase with the x axis [time] to the instant corresponding to maximum intensity* – RT)

(continued)

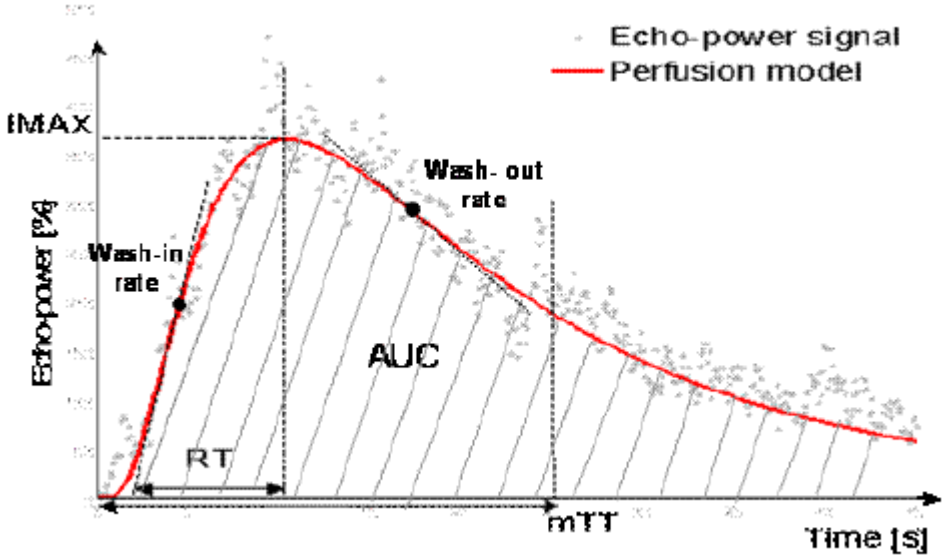
2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Evaluation Parameters (continued):

Ultrasound: Quantitative Evaluation of the Target HCC Lesion (continued) –

Representation of Contrast-Enhanced Ultrasonography Quantitative Parameters



For the primary objective of the study, variations of each quantitative parameter in the target HCC lesion at Week 2 (Visit 2) and Week 4 (Visit 3) versus baseline were to be compared to the overall tumor response at Week 8 (Visit 4) assessed by CE-MDCT/MRI, using standard RECIST criteria.

Standard Imaging Techniques (CE-MDCT/ CE-MRI plus Chest X-ray): Identification and Documentation of Tumor Lesions at Baseline – At baseline, the Investigator was to categorize tumor lesions identified by CE-MDCT (or MRI plus chest X-ray) as measurable and non-measurable as per RECIST criteria:

Measureable Lesions: To qualify as 'measurable' a lesion must have been accurately measurable in at least one dimension and its longest diameter (LD) should have been at least twice the slice thickness used (i.e., LD at baseline $\geq$20 mm using conventional measurement techniques with a contiguous slice thickness of 10 mm or $\geq$10 mm when using spiral CT scan with a contiguous slice thickness of 5 mm).

Non-measurable Lesions: Lesions considered to be 'non-measurable' included the following:

- Lesions with LD <20 mm using conventional techniques, or <10 mm using spiral CT scan;
- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion; lymphangitis cutis/pulmonis, cystic lesions; and abdominal masses that were not confirmed and followed using imaging techniques;
- Lesions situated in a previously irradiated area.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Evaluation Parameters (continued):

Standard Imaging Techniques (CE-MDCT/ CE-MRI plus Chest X-ray): Identification and Documentation of Tumor Lesions at Baseline (continued) – Up to a maximum of 5 measurable lesions per organ and 10 lesions in total were to be selected and identified as target lesions according to RECIST. These were to be measured and recorded on the CRF at baseline and followed up on. These locations should have been representative of all the organs involved, and those with the greatest LD value and suitable for accurate repeated measurements by CE-MDCT or MRI.

Target lesions selected according to RECIST criteria should have included the target HCC lesion selected for contrast-enhanced ultrasonography.

The sum of the LD for all target lesions as per RECIST criteria were to be calculated and reported as the baseline sum LD. This was to be used as a reference value for characterization of the objective tumor response.

All other lesions were to be identified as non-target lesions, and were to be recorded at baseline. Measurement of these lesions was not required and these lesions were to be followed and recorded throughout the study as "present" or "absent". The presence of any new lesion was to be recorded as well.

Standard Imaging Techniques (CE-MDCT/ CE-MRI plus Chest X-ray): Evaluation of Tumor Response as per RECIST Criteria – Response in target and non-target lesions at each on-treatment evaluation was to be evaluated according to the RECIST criteria at the investigational site as follows:

Response in Target Lesions:

- **Complete Response (CR):** The disappearance of all target lesions with no new lesions forming
- **Partial Response (PR):** At least 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum of the LD.
- **Stable Disease (SD):** The target lesions had neither sufficiently shrunk to qualify for PR, nor sufficiently increased in size to qualify for PD, taking as reference the smallest sum of the LD since treatment started.
- **Progressive Disease (PD):** At least 20% increase in the sum of the LD of the target lesions, taking as a reference the smallest sum of the LD recorded since the treatment started or the appearance of the one or more new lesions.

Response in Non-Target Lesions:

- **Complete Response (CR):** The disappearance of all non-target lesions.
- **Incomplete Response (IR)/Stable Disease (SD):** The persistence of one or more non-target lesion(s).
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

According to RECIST criteria, at the end of treatment each subject was to be assigned 'best overall response' (i.e., the best response recorded from the start of the treatment until disease progression/recurrence) as outlined in the following table:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Evaluation Parameters (continued):

Each subject's complete medical history was to be obtained and recorded within 4 weeks prior to the start of sorafenib treatment. Any concomitant medication (prescription and over-the-counter) taken by a subject from the time of signed informed consent up to study discontinuation was to be recorded on the CRF, including contrast media used for CE-MDCT/MRI examinations. Additionally, at each visit any newly prescribed pharmacological treatments were to be recorded up through the last SonoVue administration.

Subjects were to receive sorafenib monotherapy. Treatment was to be started at the recommended dosage of 400 mg (2 x 200 mg tablets) twice daily by the oral route without food (at least 1 hour before or 2 hours after a meal) or with a low-fat meal. Sorafenib treatment was to be modified as clinically indicated by an oncologist/hepatologist and at each visit any dose and regimen modifications were to be recorded on the CRF. The safety of sorafenib therapy was to be monitored as clinically indicated over the study period through clinical signs/symptoms and laboratory tests, according to standard procedures followed at each investigational site. Each subject was to remain on treatment until disease progression, subject refusal, or unacceptable toxicity occurs. Sorafenib treatment was to be continued after disease progression if clinically indicated. Further treatment was to be at the discretion of the treating physician. As the predictive values of contrast-enhanced ultrasonography for response to therapy was not demonstrated yet, treatment modifications based on contrast-enhanced ultrasonography were not to be allowed within the study.

Subjects were to be monitored for any untoward medical occurrence from the time of signed informed consent through 30 minutes after each SonoVue administration. Only postdose untoward medical occurrences occurring within 30 minutes after SonoVue administration were to be tabulated as adverse events.

A physical examination was to be performed within 4 weeks prior to the start of sorafenib treatment and before any study procedures; signs and symptoms were to be recorded on the CRF.

Vital signs (systemic blood pressure and heart rate) were to be collected just before each SonoVue administration, as well as 5 and 30 minutes after.

No laboratory evaluation was required before the administration of SonoVue in accordance to the product leaflet. However, selected laboratory test were to be assessed to exclude contraindications to the administration of contrast agents for CT or MRI examinations. Relevant data were not to be collected or analyzed for the purpose of this study.

A blood sample was to be collected within 72 hours prior to each CE-MDCT or MRI examination. The sample was to be analyzed in the local laboratory. The local laboratory was to perform the hematological and serum chemistry investigations listed below:

Hematology	**Clinical Chemistry**	
Hematocrit	Glucose	GGT
Hemoglobin	Urea Nitrogen	Uric Acid
RBC count	Creatinine	Total Protein
WBC count	Total Bilirubin	PT
Differential WBC count	AST/SGOT	PTT
Platelets	ALT/SGPT	

The Investigator or sub-investigator was to review the laboratory report before administration of the CT/MRI contrast agent.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Statistical Methods: In general, summary statistics (mean, median, standard deviation, minimum and maximum) were to be provided for continuous variables, and the number and percentage (%) of each category were to be provided for categorical data.

For subject accountability, subject completion status was to be tabulated with the number (%) of subjects enrolled up to the termination of the study, dosed with the investigational product by study visit, completed up to Week 8 (Visit 4), and any reasons for premature discontinuation of study participation were to be presented. Due to the early termination of the study, if a subject completed the assessment at Week 8 (Visit 4), that subject was considered to have completed the study.

Summary tables were to be provided for demographic and baseline characteristics, including age, sex, race, height and weight. Medical history was to be summarized by anatomical system and presented by subject in the data listings. Concomitant medications were to be coded according to therapeutic area using the World Health Organization (WHO) drug reference list. Concomitant medications recorded between signing of informed consent and follow-up were to be presented in data listings and summarized by frequency counts according to anatomical and therapeutic area for all subjects dosed. Abnormalities in physical examination were to be presented in data listings.

Descriptive statistics were to be presented to summarize the volume of investigational product administered. Dosing of SonoVue was to be summarized and listed by subject.

RECIST assessment (sum of longest diameters and response) was to be summarized at Week 8 (Visit 4).

The subjects who were evaluable for the primary end-point were defined as follows:

- those assessed by SonoVue-enhanced ultrasonography at pre-treatment and at Week 2 (Visit 2) and Week 4 (Visit 3) of therapy, with correct image acquisition for quantification;
- those assessed by the same imaging procedure (CE-MDCT or MRI plus chest X-ray) at pre-treatment and at least at Week 8 (Visit 4) of therapy;
- those with ultrasound images evaluable for off-site assessment;
- those receiving >80% of the planned sorafenib dose during the intervals between ultrasonography assessments in the initial 8 weeks of therapy (Time 0 to Week 2, Week 2 to Week 4, Week 4 to Week 8).

The primary analysis was to explore whether perfusion changes in on target HCC lesion assessed quantitatively by contrast-enhanced ultrasonography at Week 2 (Visit 2) and Week 4 (Visit 3) of sorafenib therapy could predict progression of disease at Week 8 (Visit 4) assessed by CE-MDCT/MRI, using the RECIST criteria.

The secondary analysis was to explore whether progression of the target HCC lesion determined by the Investigator based on qualitative evaluation of the contrast-enhanced ultrasonography findings at Week 2 (Visit 2) and Week 4 (Visit 3) of sorafenib therapy could predict progression of disease at Week 8 (Visit 4) assessed by CE-MDCT/MRI, using the RECIST criteria.

The various quantitative parameters were to be analyzed as exploratory and were presented by parameter and visit in listings by subject.

Due to the early termination of the study, only safety data was analyzed (selected tables were generated), all data (safety and efficacy) were presented in the listings.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Statistical Methods (continued): Adverse events were to be coded using the MedDRA coding system and were categorized by primary system organ class and preferred term, by intensity and by causal relationship to investigational product. Unique CRF verbatim terms and the MedDRA preferred terms assigned were to be listed in a matching chart.

All adverse events were to be listed. If the onset date and time information was missing, the adverse events were to be counted as postdose adverse events and were to be included in the summary. All adverse events that occurred prior to dosing were only listed in the subject data listings. If applicable, a listing was to be provided of adverse events that occurred in subjects who never received investigational product ("Enrolled but not dosed").

Investigational product-related adverse events included adverse events with 'probable', 'possible', 'unknown', and missing relationship to investigational product. Serious adverse events and adverse events leading to discontinuation were to be listed.

Adverse events with unknown onset times were to be counted as post-investigational product administration adverse events. Adverse events with unknown relation were to be counted as possibly/probably related in adverse event summary tables.

Baselines for vital signs were to be the last measurement prior to the administration of the investigational product. Vital signs (systolic blood pressure, diastolic blood pressure and heart rate) and the associated changes from baseline were to be listed.

In addition, subjects were to be flagged as having changes of potential clinical importance if values at any 2 consecutive timepoints following investigational product administration were outside the reference range and exceeded the criteria for substantial change. The changes of potential clinical importance were to be flagged ('I' for Increase or 'D' for decrease) based on the following criteria:

Parameter	**Reference Range**	**Substantial Change Criteria**
Systolic Blood Pressure (mmHg)	90-160	≥20
Diastolic Blood Pressure (mmHg)	60-90	≥10
Heart Rate (beats per minute [bpm])	60-100	≥10

Summary and Conclusions:

Summary: A total of 30 subjects were enrolled and administered at least one bolus injection of SonoVue in this study. The majority of subjects completed Week 2 (Visit 2) (27/30, 90.0%) and Week 4 (Visit 3) (25/30, 83.3%), while most subjects also completed Week 8 (Visit 4) (20/30, 66.7%). Due to the early termination of this study, only 7 subjects (23.3%) completed visits after Week 8 (Visit 4). Ten subjects discontinued the study prior to Week 8 (Visit 4): 2 subjects were considered to be ineligible (the perfusion area of the HCC lesion was <50% at baseline contrast-enhanced ultrasound); 1 subject experienced a myocardial infarction that was not reported as an adverse event; 1 subject was not a candidate for sorafenib therapy; 2 subjects could not tolerate the sorafenib therapy; 2 subjects reported a toxicity to the sorafenib therapy; and 2 subjects (Subject No. [redacted] and Subject No. [redacted]) died during the study. Both the case of myocardial infarction and the 2 cases of death occurred between scheduled study visits and outside of the protocol-defined adverse event reporting period of the previously attended study visit, therefore, none of them were reported as an adverse event nor were they attributed to the administration of SonoVue.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Summary and Conclusions (continued):

Summary (continued): The majority of subjects were male (24/30, 80%) and white (29/30, 96.7%; 1 subject was Asian). The mean age was 66.9 years (range: 33 – 80 years) with two-thirds of the subjects being ≥65 years old. The mean weight was 77.9 kg (range: 55 – 120 kg) and the mean height was 167.5 cm (range: 150 – 183 cm). All 30 subjects reported at least one abnormality in medical history with the most commonly reported being in the gastrointestinal/hepatic system (29/30, 96.7%) and cardiovascular system (17/30, 56.7%). All 30 subjects reported taking at least one concomitant medication with the most commonly reported for the cardiovascular system (27/30, 90.0%) which included diuretics and beta-blocking agents, as well as for alimentary tract and metabolism (24/30, 80/0%) which included drugs for acid-related disorders and anti-diarrheals and intestinal anti-inflammatory/anti-infective agents. One subject (Subject No. [redacted]) reported an allergy to the contrast agent for the CE-CT, although no contraindication was reported for the gadolinium agent he received during the MRI examination; the remaining 29 subjects reported having been administered at least one contrast agent for the comparison examinations (CE-MDCT/MRI), with no complications.

All 30 subjects received at least one injection of 2.4 mL of SonoVue. The table below displays the overall volume for the number (%) of subjects who received SonoVue at each visit.

	Visit 1 (N=30)*	**Visit 2** (N=27)*	**Visit 3** (N=25)*	**Visit 4** (N=21)*	**Visit 5** (N=7)*	**Visit 6** (N=3)*	**Visit 7** (N=1)*
2.4 mL (1 bolus injection)	18 (60.0)	18 (66.7)	17 (68.0)	18 (85.7)	3 (42.9)	3 (100.0)	1 (100.0)
4.8 mL (2 boli injections)	12 (40.0)	9 (33.3)	8 (32.0)	3 (14.3)	4 (57.1)	0	0

* = Number of subjects who received at least one bolus injection of SonoVue at the visit indicated.

The extent of vascularization was 100% to 75% perfused for the majority (26/30, 86.7%) of the 30 subjects at baseline (Visit 1), as it was similarly for Week 2 (Visit 2), Week 4 (Visit 3), and Week 8 (Visit 4) in 77.8% of the 27 subjects, 76.0% of the 25 subjects and 71.4% of the 21 subjects evaluated, respectively.

As displayed in the following table, enhancement was either stable or slightly reduced for the majority of subjects at each timepoint.

	Number (%) of Subjects			
Perfusion Changes Since Baseline	**Visit 1** (N=30)*	**Visit 2** (N=27)*	**Visit 3** (N=25)*	**Visit 4** (N=21)*
Enhancement Stable		18 (66.7)	19 (76.0)	18 (85.7)
Enhancement Reduced		9 (33.3)	6 (24.0)	3 (14.3)
Slight Reduction		5 (18.5)	5 (20.0)	2 (9.5)
Moderate Reduction		2 (7.4)	1 (4.0)	1 (4.8)
Marked Reduction		2 (7.4)	0	0
No enhancement		0	0	0
Enhancement Increased		0	0	0

No target lesion progression was observed for the 27 subjects evaluated at the Week 2 (Visit 2) examination nor the 25 subjects evaluated at the Week 4 (Visit 3) examination, in addition to the majority of the 21 subjects (18/21, 85.7%) evaluated at the Week 8 (Visit 4) examination.

An evaluation of tumor response per the RECIST criteria was performed and summarized for baseline (Visit -4) and Week 8 (Visit 4). The mean sum of LD of the target lesions for the 30 subjects at baseline was 125.2±62.4 mm (range: 40 – 220 mm). The mean sum of LD of the target lesions for the 21 subjects who had a Week 8 (Visit 4) evaluation was 142.8±70.1 mm (range: 43 – 272 mm). The overall response was assessed for Week 8 (Visit 4) and determined the disease to be stable for 15 of the 21 subjects (71.4%), while the remaining 6 demonstrated progressive disease.

(continued)

2 Synopsis

Name and Address of Company: Bracco Imaging S.p.A Via Folli 50 20134 Milan, Italy	**(For Bracco Regulatory Affairs Use Only) for Study BR1-129** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: SonoVue®	**Item #:**	
Name of Active Ingredient: sulfur hexafluoride microbubbles	**Item #:**	

Summary and Conclusions (continued):

Summary (continued):
One non-serious adverse event of systolic blood pressure increase was reported for Subject No. [redacted], 29 minutes after receiving one administration of 2.4 mL of SonoVue at Week 4 (Visit 3). The event was considered by the Investigator to be mild in intensity and of unknown relationship to the administration of the investigational product. The subject recovered after 1 hour. No other adverse events were reported.

Changes from each visit's pre-dose value outside of the normal reference range were observed for 9 subjects, of which only one was reported as an adverse event. The majority of these subjects' values were within normal range either at the next timepoint within that visit, or at the next visit, with the exception of 1 subject (Subject [redacted]) who did not have a subsequent visit due to the early termination of the study. None of these 9 subjects discontinued the study due to their abnormal values.

Changes from each visit's pre-dose value of potential clinical importance among the vital sign parameters were noted for 2 subjects. Subject No. [redacted] had a pre-dose systolic blood pressure of 140 mmHg which increased 25 mmHg at 5 and 30 minutes after the first injection at Week 24 (Visit 6). The subject did not receive a second bolus and, due to the termination of the study, did not return for a follow-up visit; however, no adverse event was reported for this subject. Subject No. [redacted] had a pre-dose value of 115 bpm which was outside of the normal reference range and had decreased 10 bpm at 5 and 30 minutes after the first injection of SonoVue; [redacted] heart rate was within the normal reference range at both time points after the second injection (100 bpm).

Conclusions: This study was terminated early due to slow subject enrolment; therefore, there were no formal analyses performed to correlate quantitative data with the overall tumor response based on RECIST criteria. Only 30 of the planned 168 subjects were enrolled and received at least one administration of 2.4 mL of SonoVue. Enhancement was stable for the majority of subjects at each visit. No target lesion progression was observed for all subjects at Week 2 (Visit 2) or Week 4 (Visit 3), as well as for the majority of subjects at Week 8 (Visit 4). The overall tumor response according to the RECIST criteria was assessed for Week 8 (Visit 4) and determined that the disease was stable for 15 of the 21 subjects (71.4%). One non-serious adverse event of systolic blood pressure increase was reported, which resolved without sequelae and was considered by the Investigator to be of unknown relationship to the administration of SonoVue.

Date of Report: 13 September 2011