Clinical trial results:
Characterization of Focal Liver Lesions with SonoVue®-Enhanced Ultrasound Imaging: A Phase III, Intrapatient Comparative Study Versus Unenhanced Ultrasound Imaging Using Histology or Combined Imaging/Clinical Data As Truth Standard

Summary

EudraCT number	2010-022730-91
Trial protocol	DE
Global end of trial date	29 July 2013

Results information

Result version number	v1 (current)
This version publication date	30 December 2016
First version publication date	30 December 2016

Trial information

Trial identification

Sponsor protocol code	BR1-130

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00829413
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Diagnostics, Inc.
Sponsor organisation address	259 Prospect Plains Rd, Cranbury, United States, 08512
Public contact	Maria Luigia Storto, Bracco Imaging S.p.A., (609) 514-2200, MariaLuigia.Storto@diag.bracco.com
Scientific contact	Maria Luigia Storto, Bracco Imaging S.p.A., (609) 514-2200, MariaLuigia.Storto@diag.bracco.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the sensitivity and specificity of Sonovue-enhanced ultrasound is superior to that of unenhanced ultrasound for the characterization of benign versus malignant focal liver lesions (FLLs) using final diagnosis based on histology or combiend imaging (CE-CT and/or CE-MRI)/clinical data as truth standard.

Protection of trial subjects:

This study was conducted in compliance with Title 21, CFR Part 50, CFR Part 56, and CFR Part 312, with the ethical principles that have their origin in the Declaration of Helsinki (adopted by the 18th World Medical Assembly (WMA) in Helsinki, Finland [June 1964] and amended by the 29th WMA in Tokyo, Japan [October 1975], by the 35th WMA in Venice, Italy [October 1983], by the 41st WMA in Hong Kong [September 1989], by the 48th Assembly of the WMA in Somerset West, Republic of South Africa [October 1996], by the 52nd WMA in Edinburgh, Scotland [October 2000], with clarification by the 53rd WMA in Washington DC, United States [2002] and 55th WMA General Assembly in Tokyo, Japan [2004], and by the 59th WMA General Assembly in Seoul, Korea [October 2008]). In addition, this study was conducted in compliance with Good Clinical Practices (GCP) as outlined in International Conference on Harmonization (ICH) E6 Good Clinical Practice: Consolidated Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	United States: 185
Country: Number of subjects enrolled	Germany: 108
Country: Number of subjects enrolled	France: 4
Worldwide total number of subjects	340
EEA total number of subjects	112

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	238
From 65 to 84 years	101
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date (first subject enrolled): 15 June 2010; Study completion date (last patient completed study related activities): 18 February 2013. The study was conducted at 11 investigational sites throughout the United States (USA), 2 sites in Canada and 5 sites in Europe.

Pre-assignment

Screening details:

A total of 67 patients received SonoVue in the training phase and were included only in safety population. A total of 273 patients received SonoVue in the efficacy phase. A total of 340 patients received SonoVue and are included in all safety analyses.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	UE-US (Reader 1)

Arm description:

Unenhanced Ultrasound Image Assessment by Reader 1

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	CE-US (Reader 1)

Arm description:

SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 1

Arm type	Experimental
Investigational medicinal product name	SonoVue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

SonoVue (2.4 mL bolus injection containing 8 µL/mL of sulfur hexafluoride microbubbles) was administered intravenously through an intravenous 20-guage catheter positioned into an upper extremity vein or through a central venous catheter (internal jugular vein, subclavian vein) without an IV filter Immediately following, 5 to 10 mL of saline was administered to flush the IV line of any remaining contrast agent.
A maximum of 2 injections of 2.4 mL of SonoVue was allowed with an interval of 30 minutes between the administrations.

Arm title	UE-US (Reader 2)

Arm description:

Unenhanced Ultrasound Image Assessment by Reader 2

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	CE-US (Reader 2)

Arm description:

SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 2

Arm type	Experimental

Investigational medicinal product name	SonoVue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

SonoVue (2.4 mL bolus injection containing 8 µL/mL of sulfur hexafluoride microbubbles) was administered intravenously through an intravenous 20-guage catheter positioned into an upper extremity vein or through a central venous catheter (internal jugular vein, subclavian vein) without an IV filter Immediately following, 5 to 10 mL of saline was administered to flush the IV line of any remaining contrast agent.
A maximum of 2 injections of 2.4 mL of SonoVue was allowed with an interval of 30 minutes between the administrations.

Arm title	UE-US (Reader 3)

Arm description:

Unenhanced Ultrasound Image Assessment by Reader 3

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	CE-US (Reader 3)

Arm description:

SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 3

Arm type	Experimental
Investigational medicinal product name	SonoVue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

SonoVue (2.4 mL bolus injection containing 8 µL/mL of sulfur hexafluoride microbubbles) was administered intravenously through an intravenous 20-guage catheter positioned into an upper extremity vein or through a central venous catheter (internal jugular vein, subclavian vein) without an IV filter Immediately following, 5 to 10 mL of saline was administered to flush the IV line of any remaining contrast agent.
A maximum of 2 injections of 2.4 mL of SonoVue was allowed with an interval of 30 minutes between the administrations.

Arm title	UE-US

Arm description:

UE-US Inter-reader agreement

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	CE-US

Arm description:

CE-US Inter-reader agreement

Arm type	Experimental
Investigational medicinal product name	SonoVue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

SonoVue (2.4 mL bolus injection containing 8 µL/mL of sulfur hexafluoride microbubbles) was administered intravenously through an intravenous 20-guage catheter positioned into an upper extremity vein or through a central venous catheter (internal jugular vein, subclavian vein) without an IV filter Immediately following, 5 to 10 mL of saline was administered to flush the IV line of any remaining contrast agent.

A maximum of 2 injections of 2.4 mL of SonoVue was allowed with an interval of 30 minutes between the administrations.

Number of subjects in period 1	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)
Started	259	259	259
Completed	259	259	259

Number of subjects in period 1	CE-US (Reader 2)	UE-US (Reader 3)	CE-US (Reader 3)
Started	259	259	259
Completed	259	259	259

Number of subjects in period 1	UE-US	CE-US
Started	259	259
Completed	259	259

Baseline characteristics

Reporting groups	
Reporting group title	UE-US (Reader 1)
Reporting group description: Unenhanced Ultrasound Image Assessment by Reader 1	
Reporting group title	CE-US (Reader 1)
Reporting group description: SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 1	
Reporting group title	UE-US (Reader 2)
Reporting group description: Unenhanced Ultrasound Image Assessment by Reader 2	
Reporting group title	CE-US (Reader 2)
Reporting group description: SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 2	
Reporting group title	UE-US (Reader 3)
Reporting group description: Unenhanced Ultrasound Image Assessment by Reader 3	
Reporting group title	CE-US (Reader 3)
Reporting group description: SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 3	
Reporting group title	UE-US
Reporting group description: UE-US Inter-reader agreement	
Reporting group title	CE-US
Reporting group description: CE-US Inter-reader agreement	

Reporting group values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)
Number of subjects	259	259	259
Age categorical Units: Subjects			
Adults (18-64 years)	185	185	185
Adults (>= 65 years)	74	74	74
Age continuous Units: years			
arithmetic mean	56.9	56.9	56.9
standard deviation	± 13.4	± 13.4	± 13.4
Gender categorical Units: Subjects			
Female	123	123	123
Male	136	136	136

Reporting group values	CE-US (Reader 2)	UE-US (Reader 3)	CE-US (Reader 3)
Number of subjects	259	259	259
Age categorical Units: Subjects			
Adults (18-64 years)	185	185	185
Adults (>= 65 years)	74	74	74

Age continuous			
Units: years			
arithmetic mean	56.9	56.9	56.9
standard deviation	± 13.4	± 13.4	± 13.4
Gender categorical			
Units: Subjects			
Female	123	123	123
Male	136	136	136

Reporting group values	UE-US	CE-US	Total
Number of subjects	259	259	259
Age categorical			
Units: Subjects			
Adults (18-64 years)	185	185	185
Adults (>= 65 years)	74	74	74
Age continuous			
Units: years			
arithmetic mean	56.9	56.9	
standard deviation	± 13.4	± 13.4	-
Gender categorical			
Units: Subjects			
Female	123	123	123
Male	136	136	136

End points

End points reporting groups

Reporting group title	UE-US (Reader 1)
Reporting group description:	
Unenhanced Ultrasound Image Assessment by Reader 1	
Reporting group title	CE-US (Reader 1)
Reporting group description:	
SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 1	
Reporting group title	UE-US (Reader 2)
Reporting group description:	
Unenhanced Ultrasound Image Assessment by Reader 2	
Reporting group title	CE-US (Reader 2)
Reporting group description:	
SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 2	
Reporting group title	UE-US (Reader 3)
Reporting group description:	
Unenhanced Ultrasound Image Assessment by Reader 3	
Reporting group title	CE-US (Reader 3)
Reporting group description:	
SonoVue Contrast Enhanced Ultrasound Image Assessment by Reader 3	
Reporting group title	UE-US
Reporting group description:	
UE-US Inter-reader agreement	
Reporting group title	CE-US
Reporting group description:	
CE-US Inter-reader agreement	

Primary: Sensitivity

End point title	Sensitivity[1]

End point description:

Sensitivity of SonoVue-enhanced versus unenhanced ultrasound for characterization of malignant focal liver lesions (FLLs), using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow up

End point type	Primary

End point timeframe:

24 hours to 6 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, statistical comparison between UE-US and CE-US was performed for each reader.
Finally, each reader assessed the images for 259 subjects. Therefore, 259 subjects composed each statistical analysis and not the "Subjects in this analysis: 518" field computed by the EudraCT system.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (confidence interval 95%)				
Lesions	48.7 (39.8 to 57.7)	86.6 (80.4 to 92.7)	35.3 (26.7 to 43.9)	75.6 (67.9 to 83.3)

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (confidence interval 95%)				
Lesions	16 (9.4 to 22.5)	91.6 (86.6 to 96.6)		

Statistical analyses

Statistical analysis title	Reader 1 – UE-US, Reader 1 CE-US
Comparison groups	UE-US (Reader 1) v CE-US (Reader 1)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Sensitivity (%)
Point estimate	37.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.4
upper limit	48.2

Notes:

[2] - 259 subjects in the analysis

Statistical analysis title	Reader 2 – UE-US, Reader 2 CE-US
Comparison groups	UE-US (Reader 2) v CE-US (Reader 2)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Sensitivity (%)
Point estimate	40.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	30.4
upper limit	50.3

Notes:

[3] - 259 subjects in this analysis

Statistical analysis title	Reader 3 – UE-US, Reader 3 CE-US
Comparison groups	UE-US (Reader 3) v CE-US (Reader 3)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Sensitivity (%)
Point estimate	75.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	67.9
upper limit	83.3

Notes:

[4] - 259 subjects in the analysis

Primary: Specificity	
End point title	Specificity[5]

End point description:

Specificity of SonoVue-enhanced versus unenhanced ultrasound for characterization of benign FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow-up

End point type	Primary

End point timeframe:

24 hours to 6 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, statistical comparison between UE-US and CE-US was performed for each reader.
Finally, each reader assessed the images for 259 subjects. Therefore, 259 subjects composed each statistical analysis and not the "Subjects in this analysis: 518" field computed by the EudraCT system.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (confidence interval 95%)	62.9 (54.9 to 70.9)	70.7 (63.2 to 78.3)	54.3 (46 to 62.5)	82.9 (76.6 to 89.1)

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (confidence interval 95%)	22.1 (15.3 to 29)	72.9 (65.5 to 80.2)		

Statistical analyses

Statistical analysis title	Reader 1 – UE-US, Reader 1 - SonoVue CE-US
Comparison groups	UE-US (Reader 1) v CE-US (Reader 1)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138
Method	Mcnemar
Parameter estimate	Difference in Specificity (%)
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	18.2

Statistical analysis title	Reader 2 – UE-US, Reader 2 - SonoVue CE-US
Comparison groups	UE-US (Reader 2) v CE-US (Reader 2)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Specificity (%)
Point estimate	28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.7
upper limit	37.5

Notes:

[6] - 259 subjects in this analysis

Statistical analysis title	Reader 3 – UE-US, Reader 3 - SonoVue CE-US

Comparison groups	UE-US (Reader 3) v CE-US (Reader 3)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Specificity (%)
Point estimate	50.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	42
upper limit	59.5

Primary: Accuracy

End point title	Accuracy[7]

End point description:

The Accuracy of SonoVue-enhanced versus unenhanced ultrasound for characterization of malignant and benign FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow up

End point type	Primary

End point timeframe:

24 hours to 6 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, statistical comparison between UE-US and CE-US was performed for each reader.
Finally, each reader assessed the images for 259 subjects. Therefore, 259 subjects composed each statistical analysis and not the "Subjects in this analysis: 518" field computed by the EudraCT system.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (confidence interval 95%)	56.4 (50.3 to 62.4)	78 (72.9 to 83)	45.6 (39.5 to 51.6)	79.5 (74.6 to 84.5)

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (confidence interval 95%)	19.3 (14.5 to 24.1)	81.5 (76.7 to 86.2)		

Statistical analyses

Statistical analysis title	Reader 1 – UE-US, Reader 1 - SonoVue CE-US
Comparison groups	UE-US (Reader 1) v CE-US (Reader 1)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Accuracy (%)
Point estimate	21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	29.2

Notes:

[8] - 259 Subjects in this analysis

Statistical analysis title	Reader 2 – UE-US, Reader 2 -SonoVue CE-US
Comparison groups	UE-US (Reader 2) v CE-US (Reader 2)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Accuracy (%)
Point estimate	34
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.3
upper limit	40.7

Notes:

[9] - 259 subjects in the analysis

Statistical analysis title	Reader 3 – UE-US, Reader 3 - SonoVue CE-US
Comparison groups	UE-US (Reader 3) v CE-US (Reader 3)

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mcnemar
Parameter estimate	Difference in Accuracy (%)
Point estimate	62.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	56.1
upper limit	68.3

Secondary: Positive Predictive Value [PPV]

End point title	Positive Predictive Value [PPV][10]

End point description:

Positive Predictive Value of of SonoVue-enhanced versus unenhanced ultrasound for characterization of FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow up

End point type	Secondary

End point timeframe:

24 hours to 6 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, statistical comparison between UE-US and CE-US was performed for each reader.
Finally, each reader assessed the images for 259 subjects. Therefore, 259 subjects composed each statistical analysis and not the "Subjects in this analysis: 518" field computed by the EudraCT system.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (confidence interval 95%)	52.7 (43.4 to 62.1)	71.5 (64.2 to 78.9)	39.6 (30.3 to 48.9)	78.9 (71.5 to 86.4)

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (confidence interval 95%)	14.8 (8.7 to 21)	74.1 (67.1 to 81.2)		

Statistical analyses

Statistical analysis title	Reader 1 – UE-US, Reader 1 - SonoVue CE-US
Comparison groups	UE-US (Reader 1) v CE-US (Reader 1)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001
Method	Wald Test

Notes:

[11] - 259 Subjects in this analysis

Statistical analysis title	Reader 3 – UE-US, Reader 3 - SonoVue CE-US
Comparison groups	UE-US (Reader 3) v CE-US (Reader 3)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	Wald Test

Notes:

[12] - 259 Subjects in this analysis

Statistical analysis title	Reader 2 – UE-US, Reader 2 - SonoVue CE-US
Comparison groups	UE-US (Reader 2) v CE-US (Reader 2)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001
Method	Wald Test

Notes:

[13] - 259 Subjects in this analysis

Secondary: Negative Predictive Value [NPV]

End point title	Negative Predictive Value [NPV][14]

End point description:

Negative Predictive Value of SonoVue-enhanced versus unenhanced ultrasound for characterization of FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow up

End point type	Secondary

End point timeframe:

24 hours to 6 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, statistical comparison between UE-US and CE-US was performed for each reader.
Finally, each reader assessed the images for 259 subjects. Therefore, 259 subjects composed each statistical analysis and not the "Subjects in this analysis: 518" field computed by the EudraCT system.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (confidence interval 95%)	59.1 (51.2 to 67)	86.1 (79.8 to 92.4)	49.7 (41.8 to 57.6)	80 (73.5 to 86.5)

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (confidence interval 95%)	23.7 (16.4 to 30.9)	91.1 (85.8 to 96.4)		

Statistical analyses

Statistical analysis title	Reader 1 – UE-US, Reader 1 - SonoVue CE-US
Comparison groups	UE-US (Reader 1) v CE-US (Reader 1)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001
Method	Wald Test

Notes:

[15] - 259 subjects in this analysis

Statistical analysis title	Reader 3 – UE-US, Reader 3 - SonoVue CE-US
Comparison groups	UE-US (Reader 3) v CE-US (Reader 3)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001
Method	Wald Test

Notes:

[16] - 259 Subjects in this analysis

Statistical analysis title	Reader 2 – UE-US, Reader 2 - SonoVue CE-US
Comparison groups	UE-US (Reader 2) v CE-US (Reader 2)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001
Method	Wald Test

Notes:

[17] - 259 Subjects in this analysis

Secondary: Specific Diagnosis of Malignant FLLs

End point title	Specific Diagnosis of Malignant FLLs[18]

End point description:

SonoVue-enhanced versus unenhanced ultrasound for specific diagnosis of malignant FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population
Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow up

End point type	Secondary

End point timeframe:

24 hours to 6 months

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, no statistical comparison was performed between, UE-US and CE-US. Finally, each reader assessed the images for 259 subjects.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (not applicable)				
# of HCC by Truth Standard	47	47	47	47
# HCC(Malignant) Correctly Characterized	16	26	10	29
# of Metastasis by Truth Standard	47	47	47	47
# Metastasis Correctly Characterized	18	37	12	31

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (not applicable)				
# of HCC by Truth Standard	47	47		
# HCC(Malignant) Correctly Characterized	3	30		
# of Metastasis by Truth Standard	47	47		
# Metastasis Correctly Characterized	1	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Specific Diagnosis of Benign FLLs

End point title	Specific Diagnosis of Benign FLLs[19]

End point description:

SonoVue-enhanced versus unenhanced ultrasound for specific diagnosis of benign FLLs, using the diagnosis provided by each of the 3 off-site assessors (blinded to patient data) for the ITD population
Truth standard: CE-CT and /or CE-MRI examination OR tissue pathology/histology from surgical resection/biopsy OR 6-month follow-up

End point type	Secondary

End point timeframe:

24 hours to 6 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to EudraCT system restrictions, an arm was created for each reader's assessment of UE-US and Sonovue CE-US. For 3 readers, 6 arms were created to report the results of each image assessment. For this endpoint, no statistical comparison was performed between, UE-US and CE-US. Finally, each reader assessed the images for 259 subjects.

End point values	UE-US (Reader 1)	CE-US (Reader 1)	UE-US (Reader 2)	CE-US (Reader 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	259	259	259	259
Units: Lesions				
number (not applicable)				
# of Hemangioma by Truth Standard	52	52	52	52
# Hemangioma Correctly Characterized	28	38	30	43
# of Focal nodular hyperplasia by Truth Standard	39	39	39	39
#Focal nodular hyperplasia Correctly Characterized	15	23	8	22

End point values	UE-US (Reader 3)	CE-US (Reader 3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Lesions				
number (not applicable)				
# of Hemangioma by Truth Standard	52	52		
# Hemangioma Correctly Characterized	12	38		
# of Focal nodular hyperplasia by Truth Standard	39	39		

#Focal nodular hyperplasia Correctly Characterized	2	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Inter-reader Agreement

End point title	Inter-reader Agreement[20]

End point description:

Kappa statistic based on an assessment of malignant or benign by unenhanced and SonoVue-enhanced ultrasonography separately and computation for the percentage agreement within two categories: "3 out of 3 readers agree" and "2 out of 3 readers agree".

End point type	Secondary

End point timeframe:

24 hours to 6 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to restrictions with the EudraCT system, two additional arms were created to present data for inter-reader agreement between UE-US and CE-US. For this endpoint, no statistical comparison was performed between, UE-US and CE-US.
Finally, each reader assessed the images for 259 subjects.

End point values	UE-US	CE-US		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Percentage				
number (not applicable)				
% Agreement: All 3 off-site readers agree	28.2	66		
% Agreement: 2 out of 3 off-site readers agree	94.6	99.6		
Generalized Kappa Value	0.191	0.553		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from the time of signing the Informed Consent Form through 7 days after SonoVue administration.

Adverse event reporting additional description:

All adverse events collected were categorized using MedDRA 12.1 and tabulated

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 340 (1.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colon cancer metastatic			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
rectal haemorrhage			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
hepatic hemorrhage			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
dehydration			

subjects affected / exposed	1 / 340 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 340 (12.94%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Injection site irritation			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 340 (0.59%)		
occurrences (all)	2		
Injection site haemorrhage			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	2 / 340 (0.59%)		
occurrences (all)	2		
Malaise			

subjects affected / exposed occurrences (all)	1 / 340 (0.29%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 2 / 340 (0.59%) 2		
Psychiatric disorders Hallucination subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1		
Investigations Basophil count increased subjects affected / exposed occurrences (all) Electrocardiogram abnormal subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia	 3 / 340 (0.88%) 3 		

subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 340 (1.76%)		
occurrences (all)	6		
Paraesthesia			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal tenderness			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Diarrhea			
subjects affected / exposed	4 / 340 (1.18%)		
occurrences (all)	4		
Abdominal discomfort			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 340 (0.29%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	3 / 340 (0.88%)		
occurrences (all)	3		
Dyspepsia			

subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 340 (0.59%) 2 1 / 340 (0.29%) 1 6 / 340 (1.76%) 6 2 / 340 (0.59%) 2		
Hepatobiliary disorders Hepatic pain subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1		
Renal and urinary disorders Renal pain subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Groin pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1 2 / 340 (0.59%) 2		

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 1 / 340 (0.29%) 1 1 / 340 (0.29%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2010	Amendment 1 dated 24 September 2010 included the following major changes to the protocol • The Sponsor Medical Expert and Drug Safety Physician were changed. • The number of investigational sites was increased from approximately 10 to 15. • It was possible that, in some patients, access to an upper extremity vein could be difficult; therefore the option to inject the product through a central venous catheter was added. • The possibility of an assessment of a second lesion was deleted from the protocol because these data were not relevant to the study's objectives. • Follow-up requirements for truth standard were modified to include histology as appropriate and <6 month confirmation for malignant lesions showing progression of disease on CE-MRI or CE-CT. • The CE-CT and CE-MR image acquisition parameters were modified to be consistent with current clinical practice for examination of the liver. • A statement that training cases were not to be part of the blinded read was added to the off-site assessment methodology section of the protocol to further clarify what was previously stated in the Overall Study Design Description and Statistical Methods. • The number of training cases was reduced from "up to 10" to "up to 4" and the number of efficacy cases was increased to 246 subjects to allow detection of smaller differences and to have higher statistical power for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported