



Clinical trial results:

Characterization of Focal Liver Lesions with SonoVue®-Enhanced Ultrasound Imaging: A Phase III, Inpatient 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 combined 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-gauge 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-gauge 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-gauge 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-gauge 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 standard deviation | 56.9 ± 13.4 | 56.9 ± 13.4 | 56.9 ± 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 standard deviation | 56.9 ± 13.4 | 56.9 ± 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 | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 340 (0.29%) | | |
| occurrences (all) | 1 | | |
| Flatulence | | | |
| subjects affected / exposed | 3 / 340 (0.88%) | | |
| occurrences (all) | 3 | | |
| Dyspepsia | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 24 September 2010 | <p>Amendment 1 dated 24 September 2010 included the following major changes to the protocol</p> <ul style="list-style-type: none">• 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