Clinical trial results:
MicroBubble detection and Ultrasound guided Biopsy of axillary Lymph nodes in patients with Early breast cancer.

Summary

EudraCT number	2012-001889-14
Trial protocol	GB
Global end of trial date	23 September 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	Bubble2012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	R&D Protocol Number: A092595

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Cambridge Biomedical Campus, Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Carrie Bayliss, Cambridge Clinical Trials Unit, 44 01223348158, carrie.bayliss@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge Clinical Trials Unit, 44 01223348158, carrie.bayliss@addenbrookes.nhs.uk

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	05 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2015
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Purpose of the trial: To improve the pre-operative diagnosis of axillary lymph node metastases in patients with breast cancer using an ultrasound contrast agent (SonoVue®) to detect the sentinel lymph node draining the breast and percutaneously removing it with a needle biopsy device.

Primary objective: To assess the sensitivity of the microbubble guided biopsy technique in detecting metastatic sentinel lymph nodes.

Protection of trial subjects:

Every effort was made throughout the trial to make the patient as comfortable as possible during the procedures. In Part 1 of the study, local anaesthesia of the retroareolar region at the site of the ultrasound microbubble agent was achieved with a subcutaneous injection of 2 mls 1% lidocaine. We noted that the patients in Part 1 of the study did experience a degree of discomfort during the micro bubble injection. Patients recruited to Part 2 of the study therefore had EMLA local anaesthetic cream applied to the areola 4 – 8 hours prior to the procedure, which reduced the pain experienced for this injection. For both parts of the study local anaesthetic was injected into the dermis and subcutaneous tissue of the axilla. In Part 2 of the study, prior to the vacuum assisted biopsy, a mean volume of 10mls of Lidocaine 1% and 1:200,000 adrenaline (range 5mls – 16mls) was injected into and around the axillary node prior to biopsy. Following the biopsy patients had the biopsy site compressed by hand for 10 minutes to reduce the chance of haematoma and help to minimise post biopsy discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2012
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	United Kingdom: 139
Worldwide total number of subjects	139
EEA total number of subjects	139

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	82
From 65 to 84 years	56
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited who were scheduled to undergo surgical sentinel lymph node biopsy. This was a single centre study performed by members of the Cambridge Breast Unit in Addenbrooke's Hospital, Cambridge.

Pre-assignment

Screening details:

Patients with newly diagnosed early breast cancer and recommended for SLNB as part of routine surgical management were eligible for recruitment to the study. Patients undergoing neoadjuvant chemotherapy (unless diagnosed with malignancy on VAB) were excluded from the study to avoid compromising accuracy of histological staging.

Period 1

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

Arms

Arm title	Single Arm Trial

Arm description:

This was an open-label, non-randomised study. Thus all subjects were in the single arm.

Arm type	Experimental
Investigational medicinal product name	Sulphur Hexafluoride
Investigational medicinal product code	
Other name	SonoVue
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Following local anesthesia, Sulphur Hexafluoride microbubble 0.3 mls (SonoVue™ Bracco Imaging) was injected into the dermis at the junction between the edge of the areola and the breast. SonoVue™ is composed of phospholipid stabilised microbubbles containing sulphur hexafluoride gas. It comes in powder form and is reconstituted by mixing with 2mls of (0.9%) saline. The raised "bleb" of contrast was then massaged for a few seconds to encourage passage of microbubbles into the lymphatics. If the node was not visualized then additional injections of SonoVue™ were performed up to a maximum of 3 injections with a cumulative total of not more than 1ml.

Number of subjects in period 1	Single Arm Trial
Started	139
Completed	137
Not completed	2
Became ineligible	1
Physician decision	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
All consented subjects	

Reporting group values	overall trial	Total	
Number of subjects	139	139	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	82	82	
From 65-84 years	56	56	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	61.13		
standard deviation	± 11.53	-	
Gender categorical Units: Subjects			
Female	139	139	
Male	0	0	

Subject analysis sets	
Subject analysis set title	Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects consenting to Part 1 of the study.	
Subject analysis set title	Part 2
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects consenting to Part 2 of the study.	
Subject analysis set title	Part 2 Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Consented Part 2 patients who underwent SonoVue injection and had both percutaneous biopsy and surgical pathology results excluding subjects who have chemotherapy prior to surgical excision and who are negative for malignancy at both the needle biopsy and on surgical excision. (This is due to the fact that the negative result at surgery after chemotherapy may be a false negative, as described in the protocol.)	

Reporting group values	Part 1	Part 2	Part 2 Analysis Population
Number of subjects	36	103	82
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	63.32	60.37	59.99
standard deviation	± 10.97	± 11.67	± 11.96
Gender categorical Units: Subjects			
Female	36	103	82
Male	0	0	0

End points

End points reporting groups

Reporting group title	Single Arm Trial
Reporting group description:	
This was an open-label, non-randomised study. Thus all subjects were in the single arm.	
Subject analysis set title	Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects consenting to Part 1 of the study.	
Subject analysis set title	Part 2
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects consenting to Part 2 of the study.	
Subject analysis set title	Part 2 Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Consented Part 2 patients who underwent SonoVue injection and had both percutaneous biopsy and surgical pathology results excluding subjects who have chemotherapy prior to surgical excision and who are negative for malignancy at both the needle biopsy and on surgical excision. (This is due to the fact that the negative result at surgery after chemotherapy may be a false negative, as described in the protocol.)	

Primary: Sensitivity

End point title	Sensitivity
End point description:	
Sensitivity of detecting pre-operative metastases using Microbubble Technique.	
End point type	Primary
End point timeframe:	
Overall trial	

End point values	Single Arm Trial	Part 2 Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	82[1]	82		
Units: Sensitivity				
number (confidence interval 95%)	0.58824 (0.32925 to 0.81556)	0.58824 (0.32925 to 0.81556)		

Notes:

[1] - This analysis only applies to the subjects included in the analysis population specified in the SAP.

Statistical analyses

Statistical analysis title	Primary Analysis Test

Statistical analysis description:

Test of the null hypothesis that the sensitivity is less than or equal to 10%, using a one-sided exact binomial test at the 5% significance level. A p-value is reported.

Note the analysis is not a comparison of two groups. This report lists two groups each of size 82 (and

"subjects in this analysis" as 164) due to the validation requirements of the EudraCT system to have two comparison groups.

Comparison groups	Single Arm Trial v Part 2 Analysis Population
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.00001
Method	Exact binomial test, Clopper-Pearson CIs

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events are reported from time of consent to the study.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Part 1 Safety
Reporting group description:	
All subjects in Part One who received any dose of SonoVue.	
Reporting group title	Part 2 Safety
Reporting group description:	
All subjects in Part Two who received any dose of SonoVue.	

Serious adverse events	Part 1 Safety	Part 2 Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	1 / 102 (0.98%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma	Additional description: Axillary haematoma following biopsy.		
subjects affected / exposed	0 / 35 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity	Additional description: Given routine antiobiotics at end of breast and SLN surgical operation. Went into bronchospasm, crash team called; no action required. Patient kept in overnight (due to be a daycase) as a precaution and for allergy tests. Discharged well.		
subjects affected / exposed	1 / 35 (2.86%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1 Safety	Part 2 Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	0 / 102 (0.00%)	
General disorders and administration site conditions			
Chest discomfort	Additional description: Heaviness in chest during procedure. Patient unsure whether related to procedure or heavy gardening session prior to examination. No indication that it was cardiac in origin. Resolved spontaneously.		
subjects affected / exposed	1 / 35 (2.86%)	0 / 102 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2014	The reason for the amendment was to update the safety information in the Protocol and other trial documents to bring it in line with the latest version of the Reference Safety Information. Specifically the addition of two new expected adverse reactions: hypotension and vasovagal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although sensitivity for detecting metastases is reasonable, the adverse effect of VAB on surgery is significant. We would therefore advocate the use of microbubble detection of SLN followed by core biopsy rather than VAB.

Notes: