Clinical trial results:
A Prospective Multicenter Phase III Clinical Evaluation of the Safety and Efficacy of Lumason™/SonoVue® in Subjects Undergoing Pharmacologic Stress Echocardiography with Dobutamine for the Diagnosis of Coronary Artery Disease

Summary

EudraCT number	2015-001713-28
Trial protocol	DE
Global end of trial date	25 February 2018

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	BR1-141

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02522481
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Imaging S.p.A
Sponsor organisation address	Via Folli 50, Milan, Italy, 20134
Public contact	Global Medical & Regulatory Affairs, Bracco Suisse SA, +41 228848803, patricia.caillon@bracco.com
Scientific contact	Global Medical & Regulatory Affairs, Bracco Suisse SA, +41 228848803, patricia.caillon@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	30 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2017
Global end of trial reached?	Yes
Global end of trial date	25 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective(s):
• To assess the efficacy of LUMASON/SonoVue-enhanced dobutamine stress echocardiography (DSE) in subjects with suspected or known coronary artery disease (CAD) having suboptimal left ventricular (LV) endocardial border delineation (EBD) at unenhanced echocardiography in terms of:
1) Sensitivity and specificity for the detection or exclusion of CAD in unenhanced versus SonoVue-enhanced DSE using coronary angiography or clinical follow-up as the truth standard;
2) Critical shift from suboptimal (≥2 adjacent segments inadequate on any apical view) at unenhanced dobutamine stress echocardiography (UE-DSE) to adequate images (reduction of suboptimal adjacent segments) for LV EBD at contrast-enhanced dobutamine stress echocardiography (CE-DSE).

Protection of trial subjects:

Investigators agreed to make no informal changes to the protocol, except when necessary to protect the safety, the rights or the welfare of subjects. In addition, the Sponsor ensures insurance coverage for damages concerning the subject during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2015
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	Germany: 37
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	175
EEA total number of subjects	97

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)	76
From 65 to 84 years	98
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First Patient In: 24 September 2015, Last Patient Out: 07 November 2017, Off-Site Blinded Read: 25 February 2018

Pre-assignment

Screening details:

175 subjects were enrolled, however, 2 subjects were not dosed (withdrew consent prior to dose administration), therefore, only 173 subjects were included in the Safety Population. One additional subject discontinued study participation due to a reason other than adverse event, therefore, 172 subjects completed the study.

Pre-assignment period milestones

Number of subjects started	175
Number of subjects completed	173

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2

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	LUMASON/SonoVue

Arm description:

LUMASON/SonoVue (Sulfur hexafluoride lipid-type A microspheres/Sulphur hexafluoride microbubbles) 2 mL intravenous injection

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

Dosage and administration details:

Ultrasound contrast agent administered as 2 single-dose 2-mL intravenous injections during rest and stress echocardiography

Number of subjects in period 1[1]	LUMASON/SonoVue
Started	173
Completed	172
Not completed	1
Extravasation of contrast	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 175 subjects enrolled in the study; however, 2 subjects withdrew consent prior to contrast administration leaving 173 subjects who received intravenous SonoVue.

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	173	173	
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)	76	76	
From 65-84 years	96	96	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	65.0		
standard deviation	± 10.47	-	
Gender categorical Units: Subjects			
Female	52	52	
Male	121	121	
Race Units: Subjects			
White	160	160	
Black	4	4	
Asian	5	5	
Other	4	4	
Height Units: centimetres			
arithmetic mean	169.3		
standard deviation	± 10.49	-	
Weight Units: kilograms			
arithmetic mean	86.99		
standard deviation	± 21.781	-	
Body Mass Index Units: kilograms per meters-squared			
arithmetic mean	30.33		
standard deviation	± 7.252	-	

End points

End points reporting groups

Reporting group title	LUMASON/SonoVue

Reporting group description:

LUMASON/SonoVue (Sulfur hexafluoride lipid-type A microspheres/Sulphur hexafluoride microbubbles) 2 mL intravenous injection

Subject analysis set title	Sensitivity for Detection or Exclusion of CAD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The diagnostic performance of the echocardiographic images was compared to the truth standard to determine sensitivity and specificity. A diagnosis of coronary artery disease (CAD) was determined for both the echo images and truth standard (positive diagnosis for CAD is defined as >/= 50% stenosis of any vessel on coronary angiography or if no coronary angiography is performed the occurrence of a cardiac event based on clinical information for up to 6 months post dose; otherwise the diagnosis is negative).
Results for sensitivity are reflected based on difference between contrast enhanced stress echo and unenhanced stress echo. Results for analysis of data based on majority assessment from the three off-site blinded readers are presented.
Sensitivity is the percentage of correctly diagnosed subjects by stress echo over the total positive subjects according to the truth standard.

Subject analysis set title	Specificity for Detection or Exclusion of CAD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The diagnostic performance of the echocardiographic images was compared to the truth standard to determine sensitivity and specificity. A diagnosis of coronary artery disease (CAD) was determined for both the echo images and truth standard (positive diagnosis for CAD is defined as >/= 50% stenosis of any vessel on coronary angiography or if no coronary angiography is performed the occurrence of a cardiac event based on clinical information for up to 6 months post dose; otherwise the diagnosis is negative).
Results for specificity are reflected based on difference between contrast enhanced stress echo and unenhanced stress echo. Results for analysis of data based on majority assessment from the three off-site blinded readers are presented.
Specificity is the percentage of correctly diagnosed subjects by stress echo over the total negative subjects according to the truth standard.

Subject analysis set title	Critical Shift from Sub- to Optimal Echocardiographic Images
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Reader-Specific Percentages of Participants Identified as having a Critical Shift from Suboptimal to Optimal Echocardiographic Images
The percentage of subjects with suboptimal images (defined as >= 2 adjacent segments with inadequate left ventricular endocardial border delineation (LV EBD) in any of the 3 apical views) at unenhanced stress echo converted to adequate (reduction of suboptimal segments in any of the 3 apical views) at contrast-enhanced stress echo.
Analysis population for EBD included all subjects who received LUMASON/SonoVue and had EBD data available at peak stress for both UE-DSE and CE-DSE.

Subject analysis set title	Total LV EBD (Unenhanced)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Analysis population for EBD included all subjects who received LUMASON/SonoVue and had EBD data available at peak stress for both UE-DSE and CE-DSE.

Subject analysis set title	Total LV EBD (Contrast-enhanced)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Analysis population for EBD included all subjects who received LUMASON/SonoVue and had EBD data available at peak stress for both UE-DSE and CE-DSE.

Subject analysis set title	Change in Total LV EBD (Difference [CE-DSE - UE-DSE])
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Analysis population for EBD included all subjects who received LUMASON/SonoVue and had EBD data available at peak stress for both UE-DSE and CE-DSE.

Subject analysis set title	Dummy set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

EudraCT does not allow single arm/group statistical analysis. Due to the limitations with the EudraCT system, a Dummy set was created and used as a comparison group. This dummy set is a work-around to that limitation. No subjects in this set.

Primary: Sensitivity for Detection or Exclusion of Coronary Artery Disease (CAD)

End point title	Sensitivity for Detection or Exclusion of Coronary Artery Disease (CAD)

End point description:

Analysis population for coronary artery disease (CAD) included all subjects who received LUMASON/SonoVue, had overall diagnostic conclusion of CAD available at peak stress for both unenhanced dobutamine stress echocardiography (UE-DSE) and contrast-enhanced dobutamine stress echocardiography (CE-DSE) and had a definite truth standard diagnosis (Positive, Negative) for CAD (coronary angiography or 6 months collection of cardiac events follow-up data).

End point type	Primary

End point timeframe:

Participants were followed until they had coronary angiography or up to 6 months post dose to collect clinical information on cardiac events if no coronary angiography was performed.

End point values	Sensitivity for Detection or Exclusion of CAD	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	1[1]		
Units: Percentage of Participants				
number (not applicable)	8.0	0		

Notes:

[1] - Due to limitations with the EudraCT system, a Dummy set was created as a comparison group. N=0.

Statistical analyses

Statistical analysis title	Difference between CE-DSE and UE-DSE

Statistical analysis description:

Analysis population for coronary artery disease (CAD) included all subjects who received Lumason/SonoVue, had overall diagnostic conclusion of CAD available at peak stress for both UE-DSE and CE-DSE and had a definite truth standard diagnosis (Positive, Negative) for CAD (coronary angiography or 6 months collection of cardiac events follow-up data).

Comparison groups	Sensitivity for Detection or Exclusion of CAD v Dummy set
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0896
Method	Mcnemar

Notes:

[2] - Difference between contrast-enhanced dobutamine stress echo (CE-DSE) and unenhanced dobutamine stress echo (UE-DSE) (CE-DSE - UE-DSE)

EudraCT does not allow single arm/group statistical analysis. Due to the limitations with the EudraCT

system, a Dummy set was created and used as a comparison group. This dummy set is a work-around to that limitation. No subjects in this set. Therefore, N=87.

Primary: Specificity for Detection or Exclusion of Coronary Artery Disease (CAD)

End point title	Specificity for Detection or Exclusion of Coronary Artery Disease (CAD)

End point description:

Analysis population for coronary artery disease (CAD) included all subjects who received Lumason/SonoVue, had overall diagnostic conclusion of CAD available at peak stress for both unenhanced dobutamine stress echocardiography (UE-DSE) and contrast-enhanced dobutamine stress echocardiography (CE-DSE) and had a definite truth standard diagnosis (Positive, Negative) for CAD (coronary angiography or 6 months collection of cardiac events follow-up data).

End point type	Primary

End point timeframe:

Participants were followed until they had coronary angiography or up to 6 months post dose to collect clinical information on cardiac events if no coronary angiography was performed.

End point values	Specificity for Detection or Exclusion of CAD	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	1[3]		
Units: Percentage of Participants				
number (not applicable)	33.7	0		

Notes:

[3] - Due to limitations with the EudraCT system, a Dummy set was created as a comparison group. N=0.

Statistical analyses

Statistical analysis title	Difference between CE-DSE and UE-DSE

Statistical analysis description:

Analysis population for coronary artery disease (CAD) included all subjects who received Lumason/SonoVue, had overall diagnostic conclusion of CAD available at peak stress for both unenhanced dobutamine stress echocardiography (UE-DSE) and contrast-enhanced dobutamine stress echocardiography (CE-DSE) and had a definite truth standard diagnosis (Positive, Negative) for CAD (coronary angiography or 6 months collection of cardiac events follow-up data).

Comparison groups	Specificity for Detection or Exclusion of CAD v Dummy set
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Mcnemar

Notes:

[4] - Difference between contrast-enhanced dobutamine stress echocardiography (CE-DSE) and unenhanced dobutamine stress echocardiography (UE-DSE) (CE-DSE - UE-DSE)

EudraCT does not allow single arm/group statistical analysis. Due to the limitations with the EudraCT system, a Dummy set was created and used as a comparison group. This dummy set is a work-around to that limitation. No subjects in this set. Therefore, N=83.

Primary: Critical Shift from Suboptimal to Optimal Echocardiographic Images

End point title	Critical Shift from Suboptimal to Optimal Echocardiographic

	Images[5]

End point description:

The percentage of subjects with suboptimal images (defined as >=2 adjacent segments with inadequate left ventricular endocardial border delineation [LV EBD] in any of the 3 apical views) at unenhanced stress dobutamine echocardiography (UE-DSE) converted to adequate (reduction of suboptimal segments in any of the 3 apical views) at contrast-enhanced stress dobutamine echocardiography (CE-DSE).

End point type	Primary

End point timeframe:

Participants were followed until they had coronary angiography or up to 6 months post dose to collect clinical information on cardiac events if no coronary angiography was performed.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

End point values	Critical Shift from Sub- to Optimal Echocardiographic Images			
Subject group type	Subject analysis set			
Number of subjects analysed	167			
Units: Percentage of Participants				
number (confidence interval 95%)				
Reader 1 (CE-DSE)	84.4 (74.4 to 91.7)			
Reader 2 (CE-DSE)	93.7 (87.9 to 97.2)			
Reader 3 (CE-DSE)	78.8 (67.0 to 87.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total LV EBD

End point title	Change in Total LV EBD

End point description:

Measured as the change in the total left ventricular endocardial border delineation (LV EBD) score based on the 17 segments, from peak stress unenhanced versus peak stress contrast-enhanced. Total LV EBD score ranges from 0 to 34 and higher score is better outcome.

End point type	Secondary

End point timeframe:

Participants were followed until they had coronary angiography or up to 6 months post dose to collect clinical information on cardiac events if no coronary angiography was performed.

End point values	Total LV EBD (Unenhanced)	Total LV EBD (Contrast-enhanced)	Change in Total LV EBD (Difference [CE-DSE - UE-DSE])	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	167	167	167	
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Reader 1	17.5 (± 10.83)	28.1 (± 8.32)	10.6 (± 11.98)	
Reader 2	13.4 (± 8.57)	30.5 (± 4.81)	17.1 (± 7.87)	
Reader 3	17.8 (± 7.04)	23.6 (± 7.47)	5.8 (± 9.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Adverse Events

End point title	Summary of Adverse Events

End point description:

End point type	Secondary

End point timeframe:

From the time of signed informed consent up to 72 hours post dose.

End point values	LUMASON/SonoVue			
Subject group type	Reporting group			
Number of subjects analysed	173			
Units: Number of Subjects				
Number of Subjects with Adverse Events (AEs)	21			
Number of Subjects with AEs of Mild Intensity	15			
Number of Subjects with AEs of Moderate Intensity	5			
Number of Subjects with AEs of Severe Intensity	1			
Number of Subects with Serious Adverse Events	3			
Number of Subjects Who Discontinued due to AEs	0			
Number of Deaths	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) that occurred from the time the subject signed Informed Consent until 72 hours after the last administration of LUMASON/SonoVue or until the subject underwent cardiac intervention, whichever came first, were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	LUMASON/SonoVue Safety Population

Reporting group description:

All AEs that occurred from the time the subject signed the informed consent until 72 hours after the last administration of Lumason/SonoVue or until the subject underwent cardiac intervention, whichever came first, were recorded.

Serious adverse events	LUMASON/SonoVue Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 173 (1.73%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 173 (0.58%)		
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	LUMASON/SonoVue Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 173 (10.40%)		
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Electrocardiogram change			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Haematocrit increased			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Troponin increased			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Cardiac disorders			
Bifascicular block			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Ventricular tachycardia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
General disorders and administration site conditions			

Chest discomfort subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	 1 / 173 (0.58%) 1 1 / 173 (0.58%) 1		
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 173 (0.58%) 1 1 / 173 (0.58%) 1 1 / 173 (0.58%) 1 1 / 173 (0.58%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 1 / 173 (0.58%) 1		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 1 / 173 (0.58%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Gastrointestinal infection subjects affected / exposed occurrences (all) Nasopharyngitis	 1 / 173 (0.58%) 1 2 / 173 (1.16%) 2		

subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported