



Clinical trial results: MOLECULAR FLUORESCENCE-GUIDED SURGERY (MFGS) USING BEVA800 FOR THE ASSESSMENT OF TUMOR MARGINS DURING BREAST CONSERVING SURGERY OF PATIENTS WITH PRIMARY BREAST CANCER (MARGIN-II)

Summary

EudraCT number	2018-003614-40
Trial protocol	DE
Global end of trial date	13 September 2020

Results information

Result version number	v1 (current)
This version publication date	19 May 2022
First version publication date	19 May 2022

Trial information

Trial identification

Sponsor protocol code	SVB800_001
-----------------------	------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bracco Imaging SpA
Sponsor organisation address	Via Folli 50, Milan, Italy, 20134
Public contact	Paola Pianezzola, Bracco Imaging SpA, 0039 0221772324, Paola.Pianezzola@bracco.com
Scientific contact	Paola Pianezzola, Bracco Imaging SpA, 0039 0221772324, Paola.Pianezzola@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	15 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2020
Global end of trial reached?	Yes
Global end of trial date	13 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the efficacy of fluorescence imaging using the 4.5 mg of the fluorescent tracer Beva800 at reducing the rate of positive tumor margins compared to standard-of-care (SOC) breast conserving surgery (BCS);
- To obtain additional safety data on exposure of breast cancer patients to 4.5 mg Beva800.

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	14 October 2019
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: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	34
From 65 to 84 years	17

Subject disposition

Recruitment

Recruitment details:

Informed consent was collected from 14 October 2019 to 13 September 2020.

Female subjects ≥ 18 years of age able to give informed consent and comply with the protocol requirements who were scheduled to undergo breast conserving surgery.

Pre-assignment

Screening details:

51 subjects enrolled, however 2 withdrew consent prior to dose administration, therefore 49 were included in the Safety Population (SAF Pop). 4 subjects were training cases, therefore 45 included in Intent-to-Treat Population (ITT Pop).

Pre-assignment period milestones

Number of subjects started	51
Number of subjects completed	49

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	Beva800
-----------	---------

Arm description:

The diagnostic agent Beva800 is an immune-conjugate consisting of the commercially available recombinant humanized anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody bevacizumab (Avastin®, Hofmann-La Roche, Switzerland) conjugated to the commercially available N-hydroxysuccinamide ester form of the near-infrared fluorescent dye IRDye800CW (LI-COR Biosciences, Lincoln, Nebraska, USA).

The final concentration of Beva800 is 1 mg/mL in formulation buffer of 50 mM sodium phosphate and 101 mM sodium chloride at pH 7.

Arm type	Experimental
Investigational medicinal product name	Beva800
Investigational medicinal product code	
Other name	bevacizumab-IRDye800CW
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Three days prior to surgery, intravenous injection of a single bolus of 4.5 mg Beva800, corresponding to 4.5 mL of volume was administered to the subject.

Number of subjects in period 1^[1]	Beva800
Started	49
Completed	49

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: Fifty-one (51) subjects enrolled in the study, however, 2 subjects withdrew consent prior to study agent administration, therefore, only 49 subjects are included in the Overall Trial.

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description:	
The safety analysis (SAF) population consisted of all subjects, including training cases, who received an injection of the diagnostic agent Beva800 in the study. The safety analysis was based on the safety population.	

Reporting group values	Overall Trial	Total	
Number of subjects	49	49	
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)	32	32	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	60.1	-	
standard deviation	± 10.91	-	
Gender categorical			
Units: Subjects			
Female	49	49	
Male	0	0	
Race			
Units: Subjects			
White	49	49	
Black	0	0	
Asian	0	0	
Other	0	0	
Menopausal status			
Units: Subjects			
Pre-menopausal	14	14	
Surgical menopause	2	2	
Peri-menopausal (last menses < 1 year)	1	1	
Post-menopausal (last menses ≥ 1 year)	32	32	
Height			
Units: centimetre			
arithmetic mean	165.2	-	
standard deviation	± 6.11	-	
Weight			

Units: kilogram(s)			
arithmetic mean	71.38		
standard deviation	± 12.10	-	
Age at Menopause			
Units: year			
arithmetic mean	49.9		
standard deviation	± 5.23	-	

Subject analysis sets

Subject analysis set title	ITT Pop
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population is defined as the subset of subjects in the safety population (excluding the 4 training cases) for whom the surgery after administration of Beva800 was completed in the study. If needed, this population was used for sensitivity analyses.

Reporting group values	ITT Pop		
Number of subjects	45		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	31		
From 65-84 years	14		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	59.0		
standard deviation	± 10.48		
Gender categorical			
Units: Subjects			
Female	45		
Male	0		
Race			
Units: Subjects			
White	45		
Black	0		
Asian	0		
Other	0		
Menopausal status			
Units: Subjects			
Pre-menopausal	14		
Surgical menopause	2		
Peri-menopausal (last menses < 1 year)	1		

Post-menopausal (last menses \geq 1 year)	28		
---	----	--	--

Height Units: centimetre arithmetic mean standard deviation	165.8 \pm 5.69		
Weight Units: kilogram(s) arithmetic mean standard deviation	71.57 \pm 12.45		
Age at Menopause Units: year arithmetic mean standard deviation	49.8 \pm 5.53		

End points

End points reporting groups

Reporting group title	Beva800
-----------------------	---------

Reporting group description:

The diagnostic agent Beva800 is an immune-conjugate consisting of the commercially available recombinant humanized anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody bevacizumab (Avastin®, Hofmann-La Roche, Switzerland) conjugated to the commercially available N-hydroxysuccinamide ester form of the near-infrared fluorescent dye IRDye800CW (LI-COR Biosciences, Lincoln, Nebraska, USA).

The final concentration of Beva800 is 1 mg/mL in formulation buffer of 50 mM sodium phosphate and 101 mM sodium chloride at pH 7.

Subject analysis set title	ITT Pop
----------------------------	---------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The intent-to-treat (ITT) population is defined as the subset of subjects in the safety population (excluding the 4 training cases) for whom the surgery after administration of Beva800 was completed in the study. If needed, this population was used for sensitivity analyses.

Primary: Proportion of Reduction of Subjects with Positive Margin by MFGS Using Beva800 in Comparison with the SOC BCS

End point title	Proportion of Reduction of Subjects with Positive Margin by MFGS Using Beva800 in Comparison with the SOC BCS ^[1]
-----------------	--

End point description:

The proportion of reduction of subjects with positive margin by MFGS using Beva800 in comparison with the SOC BCS was estimated as follows:

$(\text{Number of subjects with positive margin from SOC BCS} - \text{Number of subjects with positive margin from MFGS}) / \text{Number of subjects with positive margin from SOC BCS} \times 100\%$

End point type	Primary
----------------	---------

End point timeframe:

After SOC BCS

Notes:

[1] - 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. The 2-sided 95% confidence interval was calculated based on the exact binomial distribution using Clopper-Pearson method. The 2-sided 95% confidence interval is 15.7%, 84.3%.

End point values	ITT Pop			
Subject group type	Subject analysis set			
Number of subjects analysed	8 ^[2]			
Units: Number of Subjects				
number (not applicable)	4			

Notes:

[2] - Number of Subjects with Positive Margin after SOC BCS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for any untoward medical occurrences from time of signing the Informed Consent Form through 30 days after Beva800 administration.

Adverse event reporting additional description:

All untoward medical occurrences were recorded in the Adverse Event section of the case report form.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23
--------------------	----

Reporting groups

Reporting group title	SAF Pop
-----------------------	---------

Reporting group description: -

Serious adverse events	SAF Pop		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Post procedural haematoma	Additional description: Post resection and haematoma removal		
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis	Additional description: Hypertensive crises		
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SAF Pop		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 49 (30.61%)		

Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Blood pressure fluctuation			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Circulatory collapse			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2		
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2 4 / 49 (8.16%) 4 1 / 49 (2.04%) 1 1 / 49 (2.04%) 1 1 / 49 (2.04%) 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