Clinical trial results:
A prospective randomized clinical trial on 90Yttrium trans-arterial radio-Embolization (Therasphere) vs. standard of care (sorafenib) for the treatment of advanced Hepatocellular carcinoma (HCC) with Portal Vein Thrombosis (PVT).

Summary

EudraCT number	2012-005375-14
Trial protocol	BE GB ES
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	16 March 2018
First version publication date	16 March 2018

Trial information

Trial identification

Sponsor protocol code	TS-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01887717
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biocompatibles UK Ltd
Sponsor organisation address	Chapman House, Farnham Business Park Weydon Lane, Farnham Surrey, United Kingdom, GU9 8QL
Public contact	Chantal Laframboise, Biocompatibles UK Ltd, Chantal.Laframboise@btgplc.com
Scientific contact	Chantal Laframboise, Biocompatibles UK Ltd, Chantal.Laframboise@btgplc.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	23 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2017
Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Assess TheraSphere's meaningful benefit in survival in comparison with the standard-of-care (sorafenib) in patients with good hepatic function and advanced hepatocellular carcinoma (HCC) associated with portal vein thrombosis (PVT).

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. No trial procedures were performed on trial participants until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the Ethics committee.

Background therapy: -

Evidence for comparator:

Patients randomized to the control group received standard-of-care sorafenib.

Actual start date of recruitment	27 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	31
EEA total number of subjects	26

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)	14
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient enrollment started on 27 Feb 2014 and was terminated prematurely on 31 Mar 2016 due to slow recruitment, after randomization of 36 patients.
Patients were enrolled at 13 centers in 6 countries (USA, BE, ES, FR, UK and IT).
Analyses of efficacy and safety were performed on the treated population of 31 patients.

Pre-assignment

Screening details:

Patients enrolled in this study had been diagnosed with PVT associated with unresectable advanced HCC and were not eligible for any curative procedure.
Screening evaluations completed 14 days prior to randomization. Upon meeting eligibility for study participation, patients were randomized 1:1 to the TheraSphere group or the control group.

Period 1

Period 1 title	overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib

Arm description:

Patients received sorafenib orally 400 mg twice daily. Medically appropriate dose adjustments and drug holidays due to adverse events (AEs) and toxicity were allowed.

Arm type	Active comparator
Investigational medicinal product name	sorafenib
Investigational medicinal product code	sorafenib
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received twice daily 400 mg, i.e. a total dose of 800 mg.

Arm title	Therasphere

Arm description:

TheraSphere was administered through the hepatic artery. Patients received TheraSphere at a dose consistent with the approved product label to the treated lobe of the liver. The target dose was 120 Gy ± 10%.

Arm type	Device
Investigational medicinal product name	Therasphere
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator, Suspension for injection
Routes of administration	Intrahepatic use

Dosage and administration details:

The target dose was 120 Gy ± 10%.

Number of subjects in period 1	Sorafenib	Therasphere
Started	16	15
Completed	8	10
Not completed	8	5
Consent withdrawn by subject	5	1
Physician decision	1	-
administrative reason	2	4

Baseline characteristics

Reporting groups	
Reporting group title	overall study period

Reporting group description:

36 patients were randomized to treatment with TheraSphere or standard-of-care sorafenib.
Analyses of efficacy endpoints were performed on the Treated Population, which comprised 31 patients.
Summaries of safety endpoints are provided on the Safety Population, which is identical to the Treated Population. Baseline characteristics are reported from the treated population only.

Reporting group values	overall study period	Total	
Number of subjects	31	31	
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)	14	14	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.8		
standard deviation	± 8.54	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	25	25	
Race Units: Subjects			
White/Caucasian	27	27	
Black/African-American	1	1	
Other	3	3	

End points

End points reporting groups

Reporting group title	Sorafenib
Reporting group description:	
Patients received sorafenib orally 400 mg twice daily. Medically appropriate dose adjustments and drug holidays due to adverse events (AEs) and toxicity were allowed.	
Reporting group title	Therasphere
Reporting group description:	
TheraSphere was administered through the hepatic artery. Patients received TheraSphere at a dose consistent with the approved product label to the treated lobe of the liver. The target dose was 120 Gy ± 10%.	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
End point type	Primary
End point timeframe:	
Overall survival was calculated as the interval between the randomization date and the date of death for any cause, with censoring at the date of last contact for patients alive.	

End point values	Sorafenib	Therasphere		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: OS - months				
median (full range (min-max))				
Median	18.2 (2.9 to 18.2)	14.5 (2.3 to 22.0)		

Attachments (see zip file)	Kaplan-Meier Plot OS (Treated Population)/Kaplan-Meier-Plot-

Statistical analyses

Statistical analysis title	Overall Survival Statistics
Comparison groups	Therasphere v Sorafenib
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8753
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.38

Notes:

[1] - A hazard ratio of <1 corresponds to a longer survival for the Therasphere group.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Safety was assessed at all visits for enrolled patients throughout the duration of the study.	
Adverse event reporting additional description:	
Safety was assessed using v 4.0 of the National Cancer Institute's Common Terminology for Adverse Events (NCI: CTAE); CTCAE v. 4.0 standards.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Sorafenib
Reporting group description:	
Patients received sorafenib orally 400 mg twice daily. Medically appropriate dose adjustments and drug holidays due to adverse events (AEs) and toxicity were allowed.	
Reporting group title	Therasphere
Reporting group description:	
TheraSphere was administered through the hepatic artery. Patients received TheraSphere at a dose consistent with the approved product label to the treated lobe of the liver. The target dose was 120 Gy ± 10%.	

Serious adverse events	Sorafenib	Therasphere	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	0 / 15 (0.00%)	
number of deaths (all causes)	8	10	
number of deaths resulting from adverse events	4	0	
Nervous system disorders			
Hepatic encephalopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza like illness			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal vascular malformation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Sorafenib	Therasphere	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	6 / 15 (40.00%)	
Injury, poisoning and procedural complications			
Excoriation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			

Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Hepatic encephalopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)	0 / 15 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 16 (31.25%)	2 / 15 (13.33%)	
occurrences (all)	6	2	
General physical health deterioration			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 16 (25.00%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 16 (50.00%)	1 / 15 (6.67%)	
occurrences (all)	11	1	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	3 / 15 (20.00%)	
occurrences (all)	2	3	

Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Ascites			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Palmar-plantar erythrodysaesthesia syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 16 (25.00%)	0 / 15 (0.00%)	
occurrences (all)	5	0	
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2013	Protocol version 2.0: Change of sponsor.
08 August 2014	Protocol version 3.0: - Change in the inclusion/exclusion criteria - Change in the statistical analysis plan - Change in number of patients planned to be included - Change in duration of the study

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.

On 23 May 2017, the Sponsor announced early termination of the study because fewer than half of the patients remained in follow-up and there was therefore little scientific value in continuing to collect data from the remaining patients in the study.

Notes: