



Clinical trial results:

“TRANSARTERIAL EMBOLIZATION ALONE VERSUS DRUG-ELUTING BEADS CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA. A RANDOMIZED CONTROLLED TRIAL”

Summary

EudraCT number	2018-000740-25
Trial protocol	IT
Global end of trial date	19 July 2023

Results information

Result version number	v1 (current)
This version publication date	20 November 2024
First version publication date	20 November 2024

Trial information

Trial identification

Sponsor protocol code	RAD-18-TAcE
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	RAD-18-TAcE: RAD-18-TAcE

Notes:

Sponsors

Sponsor organisation name	IRCCS Azienda Ospedaliero-Universitaria di Bologna
Sponsor organisation address	Via Albertoni 15, Bologna, Italy, 40138
Public contact	U.O. Radiologia , IRCCS Azienda Ospedaliero-Universitaria di Bologna, +39 051212958, matteo.renzulli@aosp.bo.it
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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 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2023
Global end of trial reached?	Yes
Global end of trial date	19 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare TTP since randomization, as recommended from expert panel opinion [26] after TAE and DEB-TACE in a homogeneous HCC patients population and using small size beads in both arms.

Protection of trial subjects:

Yes, by specific insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 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	Italy: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	43
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study involves the enrollment of patients with a HCC diagnosis, according to the guidelines of the American Association for the Study of the Liver Disease (AASLD), as in clinical practice. The enrolled patients will have to meet the inclusion criteria and sign the informed consent for the participation in this study.

Pre-assignment

Screening details:

Inclusion and exclusion criteria are assessed at the time of screening before treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DEB-TACE

Arm description:

The chemotherapy used in this arm is the Doxorubicin that will be carried into the tumor by Embozene TANDEM (Boston Scientific) microspheres. TANDEM™ embozene microspheres are made of non-resorbable, biocompatible, hydrogel microspheres, subjected to precision calibration and coated with an inorganic perfluorinate polymer (Polyzene®-F). Thanks to their design, the microspheres can be loaded with drugs, such as doxorubicin, in order to administer a local, controlled and constant dose of the drug to the tumor sites affected after embolization.

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin + TANDEM™ embozene microspheres
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection, Dispersion for injection in pre-filled syringe
Routes of administration	Intraarterial use

Dosage and administration details:

TANDEM™ embozene microspheres are available in three different sizes, in 2 ml and 3 ml volumes of product and are supplied in preloaded vials and syringes. The maximum loadable amount on the hydro-spheres 50 mg of Doxorubicina for ml. The maximum injectable dose of Doxorubicin for each treatment is 150 mg and therefore the maximum amount of microspheres that can be used for each treatment is 3 ml. The size of microspheres that will be used in this study is up to $100 \pm 25 \mu\text{m}$.

Arm title	TAE-arm
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Arm description:

The TAE will be performed with Embozene microspheres (Boston Scientific). Embozene microspheres are spherical particles of hydrogel, precisely calibrated, biocompatible, non-absorbable and coated with a perfluorinated inorganic polymer (Polyzene®-F).

To this product it is necessary to add an appropriate amount of non-ionic contrast medium in order to obtain a homogeneous suspension and with good visibility during the injection under fluoroscopy.

Arm type	Active comparator
Investigational medicinal product name	TANDEM™ embozene microspheres
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarterial use

Dosage and administration details:

Embozene microspheres are offered in vials containing 1 ml of suspended product in physiological saline solution for apyrogenic sterile transport. The total volume of the Embozene microspheres, including the transport solution, is about 7 ml.

Number of subjects in period 1	DEB-TACE	TAE-arm
Started	55	56
Completed	13	12
Not completed	42	44
Consent withdrawn by subject	1	-
Physician decision	10	5
Death	7	11
Excluded from the inclusion criteria	15	16
Lost to follow-up	9	12

Baseline characteristics

Reporting groups

Reporting group title	DEB-TACE
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Reporting group description:

The chemotherapy used in this arm is the Doxorubicin that will be carried into the tumor by Embozene TANDEM (Boston Scientific) microspheres. TANDEM™ embozene microspheres are made of non-resorbable, biocompatible, hydrogel microspheres, subjected to precision calibration and coated with an inorganic perfluorated polymer (Polyzene®-F). Thanks to their design, the microspheres can be loaded with drugs, such as doxorubicin, in order to administer a local, controlled and constant dose of the drug to the tumor sites affected after embolization.

Reporting group title	TAE-arm
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Reporting group description:

The TAE will be performed with Embozene microspheres (Boston Scientific). Embozene microspheres are spherical particles of hydrogel, precisely calibrated, biocompatible, non-absorbable and coated with a perfluorinated inorganic polymer (Polyzene®-F).

To this product it is necessary to add an appropriate amount of non-ionic contrast medium in order to obtain a homogeneous suspension and with good visibility during the injection under fluoroscopy.

Reporting group values	DEB-TACE	TAE-arm	Total
Number of subjects	55	56	111
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	25	43
From 65-84 years	37	31	68
85 years and over	0	0	0
From 18 - 64 years	0	0	0
Age continuous			
Units: years			
arithmetic mean	69.7	67.4	
standard deviation	± 9.7	± 10.0	-
Gender categorical			
Units: Subjects			
Female	6	9	15
Male	49	47	96
Child-Pugh			
Units: Subjects			
5A	26	27	53
6A	19	13	32
7B	10	16	26
MELD			
Units: Subjects			
6-9	31	21	52
10-13	21	28	49

14+	3	7	10
Number of lesions Units: Subjects			
Single	29	27	56
Oligonodular	11	13	24
Multiple	15	16	31
Bilirubin Units: mg/dL			
arithmetic mean	1.21	1.45	
standard deviation	± 0.66	± 0.66	-
Albumin Units: g/dL			
arithmetic mean	3.78	3.67	
standard deviation	± 0.49	± 0.43	-
Creatinine Units: mg/dL			
arithmetic mean	0.85	0.83	
standard deviation	± 0.24	± 0.25	-
Max dimension Units: mm			
arithmetic mean	24.7	24.4	
standard deviation	± 11.2	± 9.5	-
Days of hospitalization Units: Days			
arithmetic mean	4.62	5.20	
standard deviation	± 2.24	± 2.92	-

End points

End points reporting groups

Reporting group title	DEB-TACE
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Reporting group description:

The chemotherapy used in this arm is the Doxorubicin that will be carried into the tumor by Embozene TANDEM (Boston Scientific) microspheres. TANDEM™ embozene microspheres are made of non-resorbable, biocompatible, hydrogel microspheres, subjected to precision calibration and coated with an inorganic perfluorate polymer (Polyzene®-F). Thanks to their design, the microspheres can be loaded with drugs, such as doxorubicin, in order to administer a local, controlled and constant dose of the drug to the tumor sites affected after embolization.

Reporting group title	TAE-arm
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Reporting group description:

The TAE will be performed with Embozene microspheres (Boston Scientific). Embozene microspheres are spherical particles of hydrogel, precisely calibrated, biocompatible, non-absorbable and coated with a perfluorinated inorganic polymer (Polyzene®-F).

To this product it is necessary to add an appropriate amount of non-ionic contrast medium in order to obtain a homogeneous suspension and with good visibility during the injection under fluoroscopy.

Primary: Time to Progression after TAE and DEB-TACE

End point title	Time to Progression after TAE and DEB-TACE
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End point description:

Compare TTP since randomization, as recommended from expert panel opinion, after TAE and DEB-TACE in a homogeneous HCC patient population and using small size beads in both arms.

End point type	Primary
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End point timeframe:

24 months

End point values	DEB-TACE	TAE-arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	33		
Units: Months				
median (standard error)				
TTP	7.98 (± 3.24)	7.56 (± 3.35)		

Statistical analyses

Statistical analysis title	Time-to-event (Kaplan-Meier)
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Statistical analysis description:

Nonparametric method used to estimate the probability of survival past given time points

Comparison groups	DEB-TACE v TAE-arm
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Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 ^[1]
Method	Kaplan-Meier curve
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.522
upper limit	1.322
Variability estimate	Standard error of the mean
Dispersion value	0.92

Notes:

[1] - P-value: 0.338

Secondary: Radiologic tumor response (mRECIST)

End point title	Radiologic tumor response (mRECIST)
End point description:	
End point type	Secondary
End point timeframe:	
6 months	

End point values	DEB-TACE	TAE-arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	55		
Units: n				
Complete Response	31	27		
Partial Response	15	21		
Stable Disease	1	2		
Progressive Disease	7	5		

Statistical analyses

Statistical analysis title	Best Overall Response (BOR) at 6 months
Statistical analysis description:	
	Radiological response of the tumor assessed using dedicated criteria (modified Response Evaluation Criteria In Solid Tumors, mRECIST) was evaluated in terms of Best Overall Response at 6 months and compared in the two treatments
Comparison groups	DEB-TACE v TAE-arm

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 ^[2]
Method	Chi-squared

Notes:

[2] - P-value: 0,586

Secondary: Overall survival

End point title	Overall survival
End point description:	
Compare OS since randomization after TAE and DEB-TACE in a homogeneous HCC patient population and using small size beads in both arms.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	DEB-TACE	TAE-arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: Months				
arithmetic mean (standard error)				
OS	24.40 (± 0.69)	22.00 (± 1.07)		

Statistical analyses

Statistical analysis title	Time-to-event (Kaplan-Meier)
Statistical analysis description:	
Nonparametric method used to estimate the probability of survival past given time points	
Comparison groups	DEB-TACE v TAE-arm
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 ^[3]
Method	Kaplan-Meier curve
Parameter estimate	Hazard ratio (HR)
Point estimate	1.697
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	4.383
Variability estimate	Standard error of the mean
Dispersion value	0.67

Notes:

[3] - P-value: 0.270

Secondary: Cost effectiveness

End point title	Cost effectiveness
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End point description:

Compare cost-effectiveness of DEB-TACE vs TAE after the entire follow-up, because, if oncologic outcomes for these two procedures are equivalent, cost containment alone should be a strong reason to support a shift from TACE to TAE

End point type	Secondary
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End point timeframe:

24 months

End point values	DEB-TACE	TAE-arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	55		
Units: Days				
arithmetic mean (standard deviation)				
Days of hospitalization	4.62 (± 2.24)	5.20 (± 2.92)		

Statistical analyses

Statistical analysis title	Comparison between 2 group's means
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Statistical analysis description:

The cost-effectiveness ratio of DEB-TACE vs TAE was evaluated considering that, given the same effectiveness of the two treatments highlighted by the previous points, there was no statistically significant difference in terms of hospitalization days between DEB-TACE and TAE, but a treatment price of the former significantly higher than the latter would lead to the suggestion of using TAE treatment instead of TACE as it is more advantageous in economic terms without losing effectiveness.

Comparison groups	DEB-TACE v TAE-arm
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Number of subjects included in analysis	105
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Analysis specification	Pre-specified
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Analysis type	equivalence
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P-value	> 0.05 [4]
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Method	Wilcoxon (Mann-Whitney)
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Parameter estimate	Mean difference (final values)
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Point estimate	0.55
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-1.713
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upper limit	0.553
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Variability estimate	Standard deviation
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Dispersion value	0
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Notes:

[4] - P-value: 0.638

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	DEB-TACE
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Reporting group description: -

Reporting group title	TAE-arm
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Reporting group description: -

Serious adverse events	DEB-TACE	TAE-arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 55 (5.45%)	2 / 56 (3.57%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Removal of common bile duct stones			

subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Liver abscess			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (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: 0.04 %

Non-serious adverse events	DEB-TACE	TAE-arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Biliary stenosis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2019	Amendment of core documents at the request of the local Ethics Committee
12 April 2023	Change of Principal Investigator in the coordinating site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported