Official title:

Prospective, Multicenter, Non Randomized, Single Arm Study to Evaluate Safety of Transarterial Chemoembolization (TACE) With Doxorubicin Eluting 100 µ Microspheres in Patients With Non Resectable Hepatocellular Carcinoma

ClinicalTrials.gov ID: NCT02670122

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Hepatocelular Multicenter prospective study of drug-eluting bead chemoembolisation safety using tightly calibrated small microspheres in non-resectable hepatocellular carcinoma

Study Code FJD-TAN-2014-01

Presented by:

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SUMMARY

Object of the investigation	Embozene TANDEM™ 100 µm microspheres
Full Title	Multicenter spanish observational, prospective study to evaluate the safety of transarterial Chemoembolisation (TACE) with tight calibrated and doxorubicin-releasing microspheres of 100 microns in the treatment of Hepatocellular Carcinoma (HCC)
Study Identifier	FJD-TAN-2014-01. Version 1.1, March 15th, 2015
Study Description	Prospective Post-authorization study of follow-up (EPA-SP)
Promotor	Dr. J. Urbano, MD, PhD Vascular and Interventional Radiology Service Ramon y Cajal University Hospital. Ctra Colmenar km 9,1 28034 MADRID -SPAIN. Phone +34 913 36 80 00 Jurbano34@salud.madrid.org
Principal Investigator	Dr. J. Urbano, MD, PhD Vascular and Interventional Radiology Service Ramon y Cajal University Hospital. Ctra Colmenar km 9,1 28034 MADRID -SPAIN. Phone +34 913 36 80 00 Jurbano34@salud.madrid.org
Primary Objective	Safety and tolerability of DEB-TACE of non-resectable HCC, using 100-µm doxorubicin-loaded microspheres
Secondary Objectives	6-, 12- and 24-month local tumor response and 2-year Over All Survival
Number of Investgators	10 Spanish University Hospitals (See annexed II)
Number of participants	130
Inclusion Criteria	Confirmed diagnosis of HCC, Subject is competent and willing to provide written informed consent, Adults (male or female) patients ≥ 18 years of age, ECOG performance status is 0 – 1 or Child-Pugh classification is A, B7, Multinodular or single nodular tumor ≥3 – 9 cm, No invasion in the major blood vessels, Proper blood, liver, renal, heart function: testing result within 2 weeks of start, No current infections requiring antibiotic therapy, Not actively on anticoagulation drugs, Measureable disease per the modified Response Evaluation Criteria in Solid Tumors (mRECIST), Life expectancy ≥ 6 months
Exclusion Criteria	(ECOG performance status ≥2; or Child-Pugh class B8 or C, Bilirubin levels >3 mg/dl, HCC with large vessel or biliary duct invasion, diffuse HCC or extrahepatic spread, Patients in which any of the following are contraindicated or present (The use of doxorubicin, MRI or CT scans, Hepatic embolization procedures, WBC < 3000 cells/mm^3, neutrophil < 1500 cells/mm^3, Cardiac ejection fraction < 50 percent, Elevated creatinine greater than or equal to 2.5 mg/dl, Impaired

	clotting test, AST and/or ALT >5x ULN or, when greater >250 U/L, Known hepatofugal blood flow, Arterio-venous shunt, Arterio-portal shunt, Main stem portal vein occlusion), Women who are pregnant or breast feeding, Allergy to iodinated contrast used for angiography, Tumor burden of more than 50% of liver, Patients with objective signs of active bacterial, viral (HIV), or fungal infection, Other primary malignancies or evidence of metastatic disease)
Enrollment Period	1 year from approval date
Clinical Visits	1 pre-treatment, 6 post-treatment (1, 3, 6, 12, 18 and 24 months)
Statistical Analysis	NA
Subject Follow-up	2 year post final treatment
Study Calendar	The study is expected to start in March 2015. The recruitment period will last 1 year, and the follow-up period 2 years, so the total duration of the study is estimated at 3 years, ending in 2018

BACKGROUND AND JUSTIFICATION OF THE STUDY

According to the guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), radiofrequency, surgery and liver transplantation are considered radical curative treatment modalities for HCC in early stage as long as they are anatomically / clinically feasible (1,3-5).
Transarterial chemoembolization (TACE) is the formal indication for the treatment of intermediate stage HCC. This treatment has a level of evidence 1 A increasing the overall survival of these patients. TACE is performed using ultraselective catheterization techniques, under high quality fluoroscopic guidance, using microcatheters. The intrahepatic artery or arteries that nourish the HCC are channeled as selectively as possible to release the therapeutic agent there (6-8).

There are considerable variations in the embolization-chemoembolization technique in relation to the choice of materials, aspects of the procedure, drug and dose used, "end point", number of sessions and space between them etc etc ... (9). There are basically two ways to apply the TACE. Conventional TACE (c-TACE), initially described in 1983, is in which lipiodol is emulsified with doxorubicin and acts as a cytostatic vehicle (10). In the past decade, synthetic microspheres have been developed that can be preloaded with doxorubicin or irinotecan drug eluting beads giving rise to TACE with microspheres (deb-TACE). This has the advantage of increasing the dose and exposure time between the neoplastic cells and the tumor while practically nullifying the systemic effect of doxorubicin. The appearance of the synthetic microspheres that are both vehicle and drug-releasing has decreased the toxicity of the treatment and has also decreased its variability (11). However, there are still many unknowns regarding the ideal TACE.

The current trend in most Western countries is to treat HCC by deb-TACE versus c-TACE. Deb-TACE has proven to be very effective in terms of local disease control, with a tendency also towards better overall survival rates although this last point has not yet been confirmed (11-15).
Regarding the ideal size of the microsphere that should be used in the hepatocarcinoma deb-TACE, there is still no consensus. This is so to the point that in the current clinical guidelines in force there is no specific recommendation in this regard (1,16-18). In the initial safety and pharmacokinetic studies conducted 10 years ago when this technique was born, microspheres between 500 and 700 microns were used (19). However, today in normal clinical practice it is considered that smaller spheres have more intratumoral penetrance. There are groups that use spheres of 300 to 500 microns (13), others that prefer those of 100 to 300 microns (14) and groups that advocate the use of spheres smaller than 100 microns (20). Experimental studies in animals have shown that reducing the size of the microspheres increases their penetration into the tumor, increasing the amount of drug released in the target tissue, thus achieving a more intense tumoricidal effect (21,22). However, ischemia and lesion of hepatic bile radicals is a potential side effect that arises if very small particles are used. A recent Italian multicenter study shows that in QETA with microspheres smaller than 100 microns (M1 DC Beads, BTG, UK) the safety and efficacy of treatment is similar or somewhat better than that published for other microsphere sizes (23). On the other hand, the recommendations and standard of treatment for QETA in liver metastases from colorectal carcinoma clearly advise the use of microspheres from 75 to 100 microns (24).

Three different brands of drug-releasing microspheres are currently approved for use in the European market. DC Beads® (BTG, Farnham, Surrey, UK), Hepasphere® (Merit Medical) and Tandem® (Celonova). Most of the literature published on "drug eluting beads" has been made using the DC Beads® platform, which currently has the largest market share. The Tandem® microspheres are of more recent commercialization (May 2012) and because of their characteristics they have a number of potential advantages although at the moment clinical studies on this product are not as abundant as on DC Beads.

In the Jiménez Díaz University Hospital, the TACE was introduced for the treatment of hepatocarcinoma in 1994. In July 2006, the first case of TACE was carried out using microspheres preloaded with doxorubicin. The experience is extensive with more than 250 treatment sessions carried out so far. In 2011 we were pioneers in Madrid in the use of the particle M1-DC Bead from 70 to 100 µ. Our usual clinical practice at this time is to use small spheres for hepatocellular carcinoma, reserving 300 or 500 micron particles only for those very bulky tumors with suspicion or evidence of arteriovenous fistulas. In March 2013, the FJD began with the use of 100µ Tandem microspheres, with 18 treatments with good results in terms of local tumor control. At the meeting on embolization that the Spanish Society of Vascular and Interventional Radiology held in Madrid last February, a consensus was reached that the 100 micron microsphere was safe and therefore its use was recommended as usual practice for the TACE of the CHC (25). In European hospitals the trend is similar using microspheres of 70 to 150µ (DC Bead M1) or microspheres calibrated of 100 or 75µ (Tandem) without so far a higher complication rate has been reported. Annex I lists the Spanish and European centers that currently use 100 or 75µ Tandem particles for the treatment using TACE of the HCC.

The TANDEM® 100µ microsphere has shown in experimental works a pharmacokinetics similar to those of DC Bead. It has a very accurate calibration compared to other microspheres in the market. It has a high loading capacity for doxorubicin and does not change its size or consistency once the drug is inside. The inflammatory reaction it causes is low thanks to the hydrogel that covers it. It is designed to penetrate deeply and homogeneously in intratumoral vascularization (26-30).

The purpose of this study is to describe the safety and tolerability of the use of Embozene TANDEM ™ microspheres in patients with unresectable HCC in whom administration of TACE is indicated.

1.1 **Embozene TANDEM™ Microspheres**

Embozene TANDEM ™ microspheres are non-absorbable, biocompatible, spherical hydrogel microparticles with a precise calibration that are coated with an inorganic perfluorinated polymer (Polyzene®-F). The microsphere design features allow Embozene TANDEM ™ microparticles to be loaded with drugs (such as doxorubicin hydrochloride and irinotecan) to deliver a constant, controlled and local dose to the embolized tumor (30).

Embozene TANDEM ™ microspheres are CE marked (CE0297) (May 2012) and are indicated for embolization under the following conditions:

- **Hepatocelular Carcinoma**
- Arteriovenous malformations
- Uterine leiomyomas
- Hypervascular tumors
- Tumors of the head, neck, torso and skeletal system
- Hemorrhages and trauma
- Presurgical tumor embolization except in the Central Nervous System

Usually **3 ml syringes with 100 µm Embozene TANDEMTM microspheres are used** (device reference number: 10730-TS0). Embozene TANDEM ™ microspheres are presented in syringes, suspended in a sterile and non-pyrogenic physiological saline solution. Embozene TANDEM ™ microsphere syringes are packed in a sterile tray sealed with a plastic film. The color-coded label indicates the size of the microsphere contained in the syringe.

1.2 Route of activation and mechanism of action

Embozene TANDEM ™ microspheres have been designed to ionically absorb and bind positively charged molecules. The antineoplastic agent doxorubicin hydrochloride is an effective positive loading drug for the treatment of HCC. This drug, when administered systemically (intravenously), has an important toxic profile that normally limits its use. After their local and selective administration in the tumor through an intra-arterial microcatheter, the microspheres release the drug (doxorubicin) in the embolitic zone by diffusion. The release of the drug depends on its physical properties, the concentration of local ions and the local pH. The released doxorubicin is then dispersed through the surrounding tissue and interacts with the metabolizing cells to inhibit duplication and ultimately kill the affected cells.

1.3 Dosage and administration

The dose of doxorubicin is the standard for TACE with 50 mg of doxorubicin per ml of microspheres. Embozene TANDEM ™ microspheres can be loaded with 98 ± 2% doxorubicin hydrochloride (in two hours, although one hour is sufficient) at room temperature. TANDEM ™ capsules loaded with doxorubicin (TANDEM ™ -DOX) remain stable for 48 hours at 4 ° C in the dark. TANDEM ™ -DOX microspheres are mixed with a contrast agent and slowly injected through an intra-arterial microcatheter into the vasculature of the tumor until stasis is achieved. The maximum dose per treatment session is 150 mg of doxorubicin in 3 ml of 100 µm TANDEM ™ doxorubicin

1 OBJECTIVES OF THE STUDY

1.1 Primary Objective

The primary objective is to evaluate the **tolerance and safety** of TACE with TANDEM ™ 100µ microspheres preloaded with doxorubicin, describing:

- Appearance and intensity of post-embolization syndrome in the 1st week after treatment
- Major adverse events during the 30 days after TACE.
- Minor adverse events during the 30 days after TACE.
- Mortality derived from treatment.

1.2 Secondary Objectives

- **Local tumor control** based on the pattern of devascularization according to RECIST 1.1 criteria (2). If a patient is referred to a liver transplant: local tumor control based on histological analysis
- ***2 year*** **overall survival** (OS)

2 STUDY DESIGN

The study has been conceived as a multicenter, international, observational, post-authorization, prospective follow-up study (EPA-SP). It is planned to include between 100 and 150 patients with non-removable HCC treated with the 100 µm Embozene TANDEM ™ microspheres (drug-releasing microparticles with doxorubicin loading) for enhanced cytotoxic transarterial embolization therapy with hepatocellular carcinoma microparticles.

10 University Hospitals of Spain with recognized experience in treatments with TACE will participate. Each center must recruit a minimum of 5 patients.

All the associated researchers are certified in Vascular and Interventional Radiology with recognized experience in liver cancer intervention, in the administration of small embolic microspheres, in the management of microcatheters and in ultraselective catheterization.

3 STUDY POPULATION

3.1 Target population

Patients with confirmed HCC and stage B according to the BCLC classification. Patients with a less advanced stage (BCLC stages 0 and A) but who are not candidates or expressly reject radical treatments with surgery or radiofrequency.

Three possible groups of patients are considered:

A.- Patients unfit for surgery or liver transplantation due to tumor extension, age and / or comorbidities.
B.- Patients not eligible for a liver transplant for exceeding the Milan criteria but with the possibility of experiencing a backward step to a previous stage (down stage) by TACE within these criteria
C.- Patients eligible for a liver transplant on the waiting list: to prevent tumor progression while on the waiting list.

3.2 Inclusion Criteria

1. Confirmed diagnosis of CHC according to EASL criteria and staged according to BCLC criteria
2. Patients with indication for TACE with 100 micron microspheres according to the usual practice of the center
3. Subjects in full power and willing to give their written informed consent to participate in the study.
4. Adult patients (men or women) ≥ 18 years of age.
5. Good quality of life. ECOG 0-1.
6. Child-Pugh preserved liver function ≤ B7.
7. Absence of tumor invasion in the main Porta vein or main bile ducts
8. Possibility of undergoing diagnostic tests with CT or MRI.
9. Liver, cardiac and renal function, preserved, with these test results in two weeks from the registration of this study:
    a. White blood cells count: > 2000 / mm2
    b. Absolute neutrophil count: > 1000 / mm3
    c. Quick Index > 50%
    d. Platelets count > 5 x 104 / mm3 and.
    e. Serum bilirubin < 3.0 mg / dL
    f. ASL, ALT 5 times within the normal range
    g. Serum creatinine <2 mg / dL
    h. Hemoglobin > 9.0 g / dL
    i. Non-unstable coronary disease or recent MI (<4 weeks)
10. Absence of concomitant infections that require antibiotic treatment.
11. Disease measurable by the modified criteria for evaluating the response in solid tumors (mRECIST 1.1).
12. Life expectancy greater than six months.

3.3 Exclusion Criteria

1. Symptomatic patient ECOG ≥ 1
2. Poor liver function, Child-Pugh ≥B8.
3. Ascites or encephalopathy
4. Extrahepatic tumor disease
5. Tumor invasion of the main portal vein
6. Serum bilirubin > 3 mg / dL
7. Cre clearance ≤ 60 mL / min
8. Patients in whom the following elements are contraindicated or present:
    a. Doxorubicin use

b. Documented allergy to iodinated contrast
c. CT and MRI scans
d. Liver embolization procedures
e. White blood cell count <2000 cells / mm3
f. Neutrophils count <1500 cells / mm3
g. Cardiac ejection fraction < 50 percent
h. Platelet count <5 x 104 / mm3, PT-INR> 2.0)
i. AST and / or ALT > 5x or when they exceed> 250 u / l
j. Known Hepatofugal blood flow
k. Gross intrahepatic A-V fistula

9. Pregnant or lactating women.
10. Tumor load greater than 50% of liver volume.
11. Active fungal or bacterial infection.
12. Other concomitant tumors.
13. Any comorbidity, condition or event that, in the opinion of the investigator, puts the patient at an undue risk that discards the use of DEB-TACE.
14. Patients who do not wish to participate and / or who refuse to give their written consent

3.4 Expected number of participants and justification

It is an observational and descriptive study. As far as we know, no data have been published in the literature on the proportion of adverse effects / complications associated with the administration of QETA with 100 micron microspheres, so it has not been possible to make a sample size predetermination based on data previous. It is intended to include 10 patients per center, which would make a total of 130 patients. With this sample size, an accuracy of 1.71% can be achieved in the estimation of a proportion through a bilateral asymptotic confidence interval of 95.00%, assuming that the proportion of the event is 1.00%.

4 STUDY DEVELOPMENT

4.1 Description of the technique

TANDEM ™ 100 µm microspheres, accurately calibrated, should fill the vasculature of the tumors when they are administered by placing the super-selective microcatheter, relocating it according to the needs and thus allowing a selective embolization on the hepatic segmental arteries of each tumor nodule.

The chemoembolization procedure is carried out under strict aseptic conditions, under conscious sedation or general anesthesia, with antibiotic prophylaxis, IV analgesia and antiemetic medication. Before chemoembolization, an angiography of the hepatic and mesenteric arteries is performed to assess the vascular anatomy of the liver, check for arteriovenous fistulas and identify the nutritional arteries of the tumor.

Chemoembolization is carried out by selective catheterization of hepatic segmental arteries with insertion into the lesion or lesions of a coaxial microcatheter. The tip of the microcatheter is located in the vessel or vessels that supply the tumor and at the same time it is checked that sufficient flow reaches the tumor (fluoroscopic verification with contrast agent). The

microcatheter should not be forced to avoid occluding or spasmodizing the nutrient artery of the tumor.

The TANDEM-DOX chemoembolization protocol (100 μm) consists of the superselective injection of a maximum of 3 ml of microspheres loaded with 50 mg / ml of doxorubicin. It will be mixed with 5-10 ml of non-ionic iodinated contrast before administration. The microspheres will be slowly injected into the vessels that water the tumors at a rate of approximately 1 ml / min. It is essential that the injection be slow to obtain the best results. The microspheres should be injected under strict real-time control with high resolution fluoroscopy.
When the flow begins to reduce, you should stop, wait a few minutes before restarting the injection. In general, the flow will increase again and an additional volume of microspheres may be administered when the microvasculature relaxes after the initial blockage. The goal is to saturate as much of the tumor bed as possible. Transarterial chemoembolization is considered a technical success when the previously established dose of drug has been administered or when the complete stasis of tumor arterial vascularization is reached. If after administering the desired dose of drug / embolization, blood flow is still detected in the tumor, no other embolizing agent or particle will be administered.

4.2 Follow-up

After the first TACE procedure, the following evaluations will be carried out:

1. Clinical and analytical control 10-20 days after discharge according to usual practice: Clinical visit in which the general condition of the patient is assessed and will be asked whether or not he had Sd. Post-pay, its duration and intensity. Analytical including blood count, coagulation tests, basic biochemistry, transaminases and bilirubin. The study may be extended with more complete imaging or analytical tests if the physician considers it necessary.
2. Dynamic liver CT or MRI every 3 m for the first 6 months and then twice a year according to usual practice.
3. Clinical and laboratory review every 3 m the first 6 months and then twice a year as usual practice until the progression, death or loss of patient follow-up, with a maximum of 5 years.
a. Quality of life assessment (ECOG)
b. Laboratory assessment
c. Evaluation of safety and efficacy and assessment of retreatment if appropriate.

5 TUMOR RESPONSE ASSESSMENT

5.1 Study Variables

Related to the patient and the disease: age, gender, etiology of liver disease, diagnosis of HCC, previous nodules treated with surgery, ablation or TACE, Child-Pugh score, BCLC stage of the tumor, size, location and number of patients. nodules, segmental vascular

invasion of the portal vein, bilioenteric shunt or previous biliary prosthesis, carrier of porto-systemic shunt, relevant concomitant pathologies.

- Variables related to the primary objective:

Post-embolization syndrome: in an adverse effect of TACE that is defined as a picture of abdominal pain, fever <38.5 ° C, and variable degree leukocytosis that appears 24 hours after the procedure and can last up to 10 days. It can be accompanied by nausea, vomiting and asthenia. It is related to tissue necrosis and is self-limited, its treatment is symptomatic. Its incidence is variable and linked to the volume of necrotic tissue.

Early adverse events derived from the procedure during the first 30 days:

1. Liver failure defined by ascitic decompensation with elevation of serum Br, jaundice and transaminases > x5 and / or hepatic encephalopathy.
2. UGIB of peptic or varicose origin
3. Intense pain that requires continued iv medication
4. High fever that is not justified by Sd. post refund
5. Liver abscess
6. Coagulative portal thrombosis
7. Acute pancreatitis
8. Acute cholecystitis
9. Renal failure, elevation of serum Cr x2 its baseline value.
10. Pleural effusion

Late adverse events arising from the procedure between the first 30 days and 6 months:

1. Intrahepatic bile duct injury defined by dilation of biliary radicals with cholestatic symptoms.

Additional therapies against cancer (sorafenib, radioembolisation, symptomatic treatment) will be documented for all patients every three months until death.

Mortality in the first 30 days after treatment

- Variables related to secondary objectives: the information will be obtained from imaging studies performed interchangeably with liver MR or CT using intravenous contrast and performing three-phase dynamic studies (arterial, portal and balance phase). Imaging studies will be evaluated according to RECIST 1.1 criteria.

    - **Tumor response**. Devascularization pattern according to RECIST 1.1 criteria. Response to treatment: The response will be classified as objective response, (OR) complete (CR), partial (RP), stable disease (EE) and tumor progression (PT) (2, 31, 32)
    - **Overall Survival** (OS)
    - **Cause of Death**: Tumor progression, complications of liver disease or others.

6 STATISTICAL ANALYSIS PLAN

6.1 Statistic analysis

A descriptive analysis of the variables included in the study will be carried out. Descriptive statistics will be calculated, including frequencies and percentages for categorical variables and means ± standard deviations or medians with interquartile ranges for continuous variables. Univariate analysis is planned to identify variables related to developing complications, using Chi-square tests. To identify risk factors related to mortality, univariate logistic regression models will be constructed. For survival analysis, Kaplan-Meier curves will be plotted, and log-rank tests are going to be used to evaluate differences between the curves. A column graph graft creation is planned to show the tumor response. In all cases where possible, the 95% confidence interval significant at $p<0.05$ will be calculated. All effects are considered. All statistical analysis will be performed with the SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

6.2 Sample Size Calculation

It is an observational and descriptive study. As far as we know, no data have been published in the literature on the proportion of adverse effects / complications associated with the administration of QETA with 100 micron microspheres, so it has not been possible to make a sample size predetermination based on data previous. It is intended to include 10 patients per center, which would make a total of 130 patients. With this sample size, an accuracy of 1.71% can be achieved in the estimation of a proportion through a bilateral asymptotic confidence interval of 95.00%, assuming that the proportion of the event is 1.00%.

7 ADVERSE EVENTS

7.1 Definition

Adverse Event is considered to be any adverse medical event that occurred to a patient or to a subject that participates in a clinical investigation even if it does not necessarily have a causal relationship with it. An Adverse Event may also be any unfavorable or unexpected sign, including an abnormal laboratory finding, symptom, or illness temporarily associated with the investigation, whether or not related to it.
This study is observational, so the patient is not exposed to a higher risk than usual clinical practice. However, as part of the descriptive study, a record of adverse events will be carried out, the rules of which are described below:

7.2 Detection and documentation

It is the responsibility of the investigator to document all adverse events that occur during the study. At each visit / evaluation, all adverse events observed by both the researcher, and one of his clinical collaborators, such as those reported by the subject spontaneously or in response to a direct question, will be evaluated by the investigator and noted in the section on Adverse events in the subject's data collection notebook.
Adverse events must be recorded at each evaluation visit throughout the study. The nature of each event, the start time after the procedure under evaluation, the duration, severity and relationship with it should be established. The details of any corrective treatment must be recorded on the corresponding pages of the data collection notebook. The initial symptomatology must be well documented at the selection visit. It is important to correctly collect the baseline information in order to interpret the data of subsequent visits.
Follow-up of adverse events: Investigators should monitor subjects with adverse events until they have decreased, disappeared or until the process has stabilized. Reports regarding the course of the evolution of the subject should be sent to the clinical trial monitor.

7.3 Severity assessment

30-day mortality, minor and major adverse events after Tandem-100 DEB-TACE were assessed in accordance with CTCAE 4.03 criteria (33)

The maximum intensity should be assigned one of the following categories:

- **Minor**: An adverse event easily tolerable by the subject, causing minimal discomfort and not interfering with daily activity.
- **Major**: Any adverse event or adverse reaction that, at any dose, causes death, threatens the life of the subject, necessitates hospitalization or prolongation of the subject, causes permanent or significant disability or disability, or results in an anomaly or congenital malformation. For the purposes of its notification, suspicions of adverse events or adverse reactions that are considered medically important will be treated as serious, even if they do not meet the above criteria.

8 ETHICAL ASPECTS

8.1 Clinical Research Ethics Committee, Institutional Review Board (IRB)

Before the implementation of this study, the protocol, the proposed informed consent form and the patient information sheets must be reviewed by the IRBs of the participating centers. The IRB of the Jiménez Díaz Foundation University Hospital will act as a Reference IRB. A signed and dated document confirming that these documents have been approved by the IRB must be delivered to the promoter, together with the name and position of the president and members of the IRB.

8.2 General considerations

This study should be carried out in accordance with the protocol and with the standards of good clinical practice, as described in:

• Harmonized Tripartite Standards of ICH E6, for Good Clinical Practice of 1996.

• Directive 2001/20 / EC.

• Declaration of Helsinki and amendments concerning medical research in humans.

• Order SAS / 3470/2009

• Biomedical Research Law 14/2007

The researcher agrees, with the signing of this protocol, to follow the instructions and procedures described therein and will therefore comply with the principles of Good Clinical Practice on which it is based. Once the protocol is signed, it should not be modified without the written agreement of both the promoter and the principal investigator, and with the consent of the Clinical Trials Ethics Committee.

8.3 Patient information

The researcher must explain to each subject the nature of the study, its purposes, procedures, expected duration and the potential risks and benefits related to participation in the study, as well as any inconvenience this may entail. Each participant should be advised that their participation in the study is voluntary and that they can leave the study at any time, without affecting their subsequent medical treatment, or their relationship with the treating doctor.

Informed consent will be provided by standard writing, in language easily understood by the participant. The subject must have sufficient time to read and understand the explanations before dating and signing the informed consent and should receive a copy of the signed document. No subject can be included in the study without previously giving their informed consent.

8.4 Confidentiality and access to data

La confidencialidad de los datos personales de los sujetos se mantendrá, aunque sujeta a la necesidad, por parte del monitor, de verificar los datos originales frente a la historia clínica del sujeto. En el cuaderno de recogida de datos y en toda la correspondencia del estudio figurará tan solo el código del paciente y el código del estudio. El promotor no guardará ningún documento con el nombre de ningún sujeto. En todo momento se respetará y cumplirá la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal.

Toda la información revelada por el promotor al investigador será tratada de manera estrictamente confidencial. El investigador solo hará uso de esta información para el estudio que se describe en este protocolo. Se compromete, además, a no revelar dicha información a terceros, salvo a otros colegas o empleados que participen en la

ejecución del estudio y que se hallen asimismo vinculados por las obligaciones de confidencialidad.

8.5 Financial Report

This study is an independent project sponsored by the Spanish Society of Vascular and Interventional Radiology (SERVEI) that does not have specific funding for its realization. This is an observational study that does not include additional procedures to those performed in routine clinical practice. Neither the study researchers nor the patients will receive any remuneration for their participation in it (economic report 0). The exemption of evaluation and administrative management fees is requested from the IRB.

9 PRACTICAL ISSUES

9.1 Responsibilities of all study team

Researcher: Researchers will follow the rules of Good Clinical Practice and will know and follow the corresponding Standardized Work Procedures. All the information collected during the study will be recorded directly in the data collection booklet, which is attached as annex I. When a correction is made, the date and initials of the person making it should be noted.

Auxiliary staff: Auxiliary staff will follow the instructions given by the researcher regarding the extraction of blood samples, their handling and other complementary examinations.

Monitor: You must attest that the information collected in the protocol is truthful, for which you must have all kinds of facilities by the research team to carry out their work.

Sponsor: He will be responsible for ensuring compliance with the relevant legal regulations and for providing the medication under study.

9.2 Protocol deviations

When a situation occurs that causes a deviation from the protocol, the deviation will be only for that subject. Researchers present in such circumstances will fully document the deviation and reason in the CRD. In the event that the deviation has to do with the inclusion / exclusion criteria, the researchers will contact the clinical monitor by telephone to inform them of such deviation.

9.3 Amendments to the protocol

Neither the investigator nor the monitor nor the sponsor will modify this protocol without first obtaining the consent of the other parties. The modification must be documented in writing. Any change in the research activity, except those necessary to eliminate an immediate apparent risk to the volunteer, must be reviewed and approved by the IRB before implementation. The promoter must send the amendments to the protocol to the health authorities, and the modifications may require the revision and approval of the IRB

9.4 Acceptance of the researcher

The researcher's commitment is included in the documentation submitted to the IRB.

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10 Annex I:

European and Spanish hospitals that regularly use TANDEM microspheres of 100 Microns or less for HCC TACE

- Alemania:

University Jena
University Heidelberg
Klinik Bogenhausen (Munich)
Städische Klinik Bonn
University Kiel
University Leipzig
Rotes Kreuz Krankenhaus Essen
Kreis Krankenhaus Kassel
St. Johannes Dortmund
Herz-Jesu Krankenhaus Hiltrup
Klinikum Ingolstadt
Klinikum Fulda

- France:

CHU Grenoble
CHU Bordeaux
CHU Lille
CHU Dijon
APHN Hopital Timone

- Italy:

Instituto di Tumori, Milano
Cancer Institute Bologna
Humanitas Hospital, Milano
Roberto Neri Hospital, Roma
San Giovanni, Addolorata
St. Maria, Ravenna
Lecco Hospital
City Hospital, Perugia
Teramo Hospital
L'Aquila Hospital

- Turkey:

Cukurova University Hospital, Adana
Hacettepe University Hospital, Ankara
Turkiye Yuksek Ihtisas Hastanesi, Ankara
Adnan Menderes University Hospital, Aydin Ankara

Numune Training and Research Hospital, Ankara
Pamukkale Universitesi Hastanesi,
Denizli Selcuk University Hospital, Konya
Eylul University Hospital, Izmir
Training and Research Hospital, Istanbul

- Spain and Portugal:

Centro hosp.e Univ.Coimbra (Portugal)
Instituto port.oncologia do Porto, Oporto (Portugal)
Complejo Asistencial Universitario de Burgos
Ruber Internacional, s.a. Madrid
Hospital Ramón y Cajal, Madrid
Fundación Jiménez Díaz, Madrid
Hospital Clínico Universitario de Valencia
Hospital General de Castellón
Hospital de Galdakao-Usansolo, Vizcaya
Hospital Lucus Augusti, Lugo
Hospital Virgen de la Salud, Toledo
Hospital Universitario Carlos Haya, Málaga
Hospital Clínico San Cecilio, Granada
Hospital Universitario Virgen del Rocío, Sevilla

11 Annex II: List of Researchers and Participating Centers

A. Andalusia

1.	Virgen del Rocío University Hospital, Sevilla	Dr. Veronica Nacarino Mejias
2.	Carlos Haya University Hospital, Málaga	Dr. J. Joaquín Muñoz Ruiz Canela

B. Galicia

3.	Lucus Augsti University Hospital, Lugo	Dr. Lucia Lopez Carreira

C. Madrid

4.	Ramón y Cajal University Hospital	Dr. José Urbano and Dr Juan Sánchez Corral
5.	Fundación Jiménez Díaz University Hospital	Dr. José Urbano
6.	Puerta de Hierro University Hospital	Dr. Rocio Gonzalez Costero
7.	La Princesa University Hospital	Dr. Julian Cuesta

D. Basque Country

8.	Galdakao General Hospital, Bilbao, Vizcaya	Dr Javier Echevarria Uraga
9.	Basurto University Hospital, Bilbao	Dr. Borja Peña Baranda

E. Castilla La Mancha

10.	Virgen de la Salud University Hospital. Toledo	Dr Juan J Ciampi Dopazo