A Single-arm Trial of Transcatheter Arterial Chemoembolization with Tandem Microspheres in the Treatment of Localized Hepatocellular Carcinoma

A Study of Tandem Microspheres in Localized Hepatocellular Carcinoma

STOPPER

CLINICAL INVESTIGATION PLAN

Study Reference Number：S2382

Sponsor By

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Vendors/Labs	Vendors/Laboratory involved in the trial is provided in the Manual of Operations.

Original Release: January 16, 2017

Current Version: March 23, 2018

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	January 16, 2017	90702637 Rev./Ver. AH	None	None	Original release
AB	May 2，2017	90702637 Rev/Ver AH	Section 5.2	Add “Device Labeling”	To be in compliance with China Medical Device GCP
AB	May 2，2017	90702637 Rev/Ver AH	Section 2 Section 9.3	Combined Exclusion Criteria #1 and #8	Remove repeated content to ensure accuracy
AB	May 2，2017	90702637 Rev/Ver AH	Section 9.3	Add Exclusion Criteria：The investigator believes the subject is not suitable for the study	To be consistent with Section2
AB	May 2，2017	90702637 Rev/Ver AH	Section 10.3	Add “ Enrollment Control”	To be in compliance with China Medical Device GCP
AB	May 2，2017	90702637 Rev/Ver AH	Section11 Table 11.1	Remove ‘Hepatitis B and C biomarker tests’ from the blood test and list as only the baseline test	Remove unnecessary tests at follow-ups
AB	May 2，2017	90702637 Rev/Ver AH	Section 11.5	Add “Post Initial Treatment”	To ensure accuracy
AB	May 2，2017	90702637 Rev/Ver AH	Section 11.6 Section 11.7 Section 118 Section 11.9	Remove ‘Hepatitis B and C biomarker tests’ from follow-up test list	Remove unnecessary tests at follow-ups
AB	May 2，2017	90702637 Rev/Ver AH	Section 11.6 Section 11.7 Section 11.8 Section 11.9	Change to ‘Plain scan plus enhanced MRI’	To ensure adequacy of imaging test for HCC
AB	May 2，2017	90702637 Rev/Ver AH	Section 11.4	Change to’Scanning sequence include coronal T2WI，transect T2WI、T1WI、DWI，enhanced scan using 3D T1WI’	To ensure adequacy of imaging test for HCC
AB	May 2，2017	90702637 Rev/Ver AH	Section 11.4	Add ‘CT scan to monitor the migration of microspheres in case of non-target embolization during treatment’	To ensure adequacy of imaging test for HCC
AB	May 2，2017	90702637 Rev/Ver AH	Section 12.3.2	Delete “Interim Analysis”	Remove irrelevant content

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AB	May 2，2017	90702637 Rev/Ver AH	Section 19.1	Add Table 19.1-1'Incidence rates of expected embolization related adverse events'	To ensure accuracy
AB	May 2，2017	90702637 Rev/Ver AH	Section 19.4	Add "Benefit-Risk Ratio"	To be in compliance with China Medical Device GCP
AB	May 2，2017	90702637 Rev/Ver AH	Section 20.3 Table 20.3-1	Change 'First aware of the event in one working day' to 'First aware of the event in 24 hours'	To be in compliance with China Medical Device GCP
AB	May 2，2017	90702637 Rev/Ver AH	Section 20.5	Delete 'CEC related description'	Remove irrelevant content
AB	May 2，2017	90702637 Rev/Ver AH	Section 12.1.1 Section 13.3 Appendix E	Add 'EASL tumor response evaluation criteria'	To ensure adequate endpoint assessment
AB	May 2，2017	90702637 Rev/Ver AH	All Chapters	Add Acronyms when it's first mentioned in the protocol	To ensure accuracy
AC	June 3, 2017	90702637 Rev/Ver AH	Section2 Section9	Change the tumor size in the inclusion criteria to 'diameter <7am for single lesion or maximum 3 lesions with total diameter less than 10cm'； Change BCLC stage from 'A/B' to 'A/B7' on inclusion criteria; Change bilirubin level from '>3mg/dl' to '>2mg/dl' on exclusion criteria	To enroll more appropriate patients
AC	June 3, 2017	90702637 Rev/Ver AH	Section 11	List detailed tests at baseline and follow-ups	To ensure accuracy
AC	June 3, 2017	90702637 Rev/Ver AH	Section 11.4 Section 11.5	Add details on imaging assessment and post-treatment evaluation	To clarify
AC	June 3, 2017	90702637 Rev/Ver AH	All Chapter	Wording	To ensure accuracy
AD	March 23, 2018	90702637 Rev/Ver AH	Contact information	Update contact person	Update project manager
AD	March 23, 2018	90702637 Rev/Ver AH	Section 8	Add "Study Flow Chart"	To clarify study flow
AD	March 23, 2018	90702637 Rev/Ver AH	Section 9.2	Add "individual diameter<7cm，maximum 3 lesions with >1cm in diameter" for multiple tumors	To clarify
AD	March 23, 2018	90702637 Rev/Ver AH	Section 9.2 & Attachment A	Change the version of HCC management guideline from 2011 to 2017	To be consistent with up to date HCC management guideline

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AD	March 23, 2018	90702637 Rev/Ver AH	Section 9.3	Change "Portal vein invasion" to "Invasion of the main or primary branches of the portal vein"	To clarify
AD	March 23, 2018	90702637 Rev/Ver AH	Section 9.3	Remove #3 "3. Prior intra-arterial embolization or chemotherapy or systemic therapy for treatment of HCC"	Redundant with #6 of the inclusion criteria
AD	March 23, 2018	90702637 Rev/Ver AH	Section 11.3	Change to "Before any study specific tests or procedures are performed" to "Before the screening procedure"	To ensure the accuracy of the description of study procedure
AD	March 23, 2018	90702637 Rev/Ver AH	Section 11.5	Delete "For subjects with bilobar involvement, each of the two lobes should be treated subsequently with the lobe with the higher tumor burden treated first"	The treatment strategy will be determined by the investigator, which is more consistent with actual clinical practice
AD	March 23, 2018	90702637 Rev/Ver AH	Section 11.10	Delete "Pass the follow-up window (14 days passed the scheduled follow-up time"	To ensure a more reasonable definition of study ending
AD	March 23, 2018	90702637 Rev/Ver AH	Attachment C	Add the measurement unit commonly used in China for serum total bilirubin and serum albumin	To facilitate Child-Pugh score
AD	March 23, 2018	90702637 Rev/Ver AH	All chapters	Wording	To ensure accuracy

2. Protocol Synopsis

<table>
<tr><td colspan="2">A Single-arm Trial of Transcatheter Arterial Chemoembolization with Tandem Microspheres in the Treatment of Localized Hepatocellular Carcinoma</td></tr>
<tr><td>Study Objective</td><td>The primary objective of this study is to evaluate the safety and efficacy of transcatheter arterial chemoembolization with Tandem Microspheres loaded with Epirubicin in the treatment of subjects with localized hepatocellular carcinoma (HCC)</td></tr>
<tr><td>Study Device</td><td>Tandem Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with Polyzene®-F, an inorganic polymer.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>Tandem Microspheres are indicated for the embolization of arteriovenous malformations and hypervascular tumors</td></tr>
<tr><td>Device Specifications</td><td>Tandem Microspheres are stored in 2 ml and 3 ml sized syringes. They are available in a range of sizes (40, 75, and 100 μm). Microspheres used will be at the discretion of the treating physician(s) based on the tumor size and/or vascular structure.
<table>
<tr><th>Microspheres Diameter（μl）</th><th>Size（ml）</th></tr>
<tr><td>40</td><td>2</td></tr>
<tr><td>40</td><td>3</td></tr>
<tr><td>75</td><td>2</td></tr>
<tr><td>75</td><td>3</td></tr>
<tr><td>100</td><td>2</td></tr>
<tr><td>100</td><td>3</td></tr>
</table></td></tr>
<tr><td>Study Design</td><td>This is a prospective, single-arm, multicenter study to evaluate the safety and efficacy of transcatheter arterial chemoembolization with Tandem Microspheres loaded with Epirubicin in the treatment of subjects with localized hepatocellular carcinoma. All qualified subjects will be enrolled in the study and receive transcatheter arterial chemoembolization treatment with Tandem Microspheres loaded with Epirubicin</td></tr>
<tr><td>Sample Size</td><td>109 subjects (including 10% loss to follow-up)</td></tr>
<tr><td>Number of Study Sites</td><td>10 clinical centers will be participating in the study</td></tr>
<tr><td>Primary Effectiveness Endpoint</td><td>The primary effectiveness endpoint for this clinical trial is 6-month objective tumor response rate (ORR).</td></tr>
</table>

Secondary Endpoints	• ORR at 30-day and 3-month • Time to Progression (TTP) • Time to Extrahepatic Spread • Proportion Progression-Free (PPF) at one year • Overall survival at one year • The frequency of Tandem treatment associated adverse events
Study Enrollment	Subject will be qualified to be enrolled in the clinical trial once signed the IRB/EC approved informed consent, meet all inclusion criteria and does not meet any of the exclusion criteria. All enrolled subjects will receive the transcatheter arterial chemoembolization with Tandem Microspheres. Enrollment timepoint will be based on subject receiving transcatheter arterial chemoembolization treatment with Tandem Microspheres loaded with Epirubicin
Follow-up Plan	Follow-up will be conducted at 30 days and 3, 6, and 12 months post initial treatment. The tests during the follow-ups include: • Laboratory (include Complete Blood Count, blood biochemistry, blood coagulation function, renal and liver function, electrolyte , AFP) and imaging tests (include plain scan plus enhanced MRI, Chest plain scan CT) at 30 days and 3, 6 and 12 months post procedure • ECG at 3 months post procedure
Study Duration	The study will end when all subjects completed the 12-month follow-up post initial treatment, or withdraw (death, loss to follow-up or withdraw consent).

Inclusion Criteria	Subjects may be included in the study only if they meet all of the following criteria: 1. Subject is able to provide informed consent and must sign the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form. 2. Male or female of age ≥18 and ≤75 years. 3. Confirmed diagnosis of HCC according to the diagnostic criteria included in the management guideline issued by China's Ministry of Health in 2017. 4. HCC is diagnosed for the first time or recurrence of tumor after surgical or ablation treatment. 5. Single tumor less than 7cm in diameter or multiple tumors with maximum 3 lesions with >1cm in diameter, individual diameter <7cm and less than 10cm in total diameter. 6. no previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy) for HCC 7. Preserved liver function (Child-Pugh A or B7). 8. ECOG Performance Status 0 or 1.

Exclusion Criteria	Subjects will be excluded for the following reasons: 1. Presence of vascular invasion or extra-hepatic spread of disease, or diffuse HCC, defined as >50% liver involvement , or arteriovenuous fistula 2. Macrovascular invasion of main or primary branches of portal vein at entry into the study 3. Any contraindication for TACE treatment 4. Any contraindication for Epirubicin administration 5. Advanced liver disease (bilirubin levels >2 mg/dl, AST or ALT >5 times upper limit of normal) 6. Renal failure or insufficient renal function (Creatinine levels >2 mg/dl) 7. Subject unable to receive MRI examination 8. Pregnant or breast feeding woman, or plan to become pregnant during treatment or within 12 months of treatment 9. couldn't commit reliable birth control measures during treatment or within 12 months of treatment 10. Subject is participating other investigational drug or device clinical trial within 30 days of signing the informed consent 11. Subject is not suitable to participate in the study as judged by investigator
Statistical Methods	
Primary Study Hypotheses	The primary hypothesis is that the 6-month ORR in the Tandem microspheres embolization and drug delivery arm is higher than the performance goal (PG). The null (H_0) and alternative (H_1) hypotheses for this primary endpoint are presented below. H_0: $P_e \leqslant PG$ H_1: $P_e > PG$ where P_e is the expected 6-month ORR (%).
Statistical Test	A normal approximation test will be used to assess the one-sided hypotheses of the test device superior to the PG

Success Criteria for the PG	The test device will be concluded to be superior to the PG in the primary analysis if the one-sided lower 97.5% confidence bound for the test device performance in 6-month ORR is greater than PG.
Sample Size Parameters	The overall sample size (N=109) is driven by the primary effectiveness endpoint. • Power ⩾ 85% • One-sided significance level = 2.5% (alpha) • PG for 6-month ORR = 45% • Expected 6-month ORR = 60% • Total N=98 subjects are required for 6-month assessment • Attrition rate = 10% (loss to follow-up in 6 months) • Approximately N=109 subjects to enroll

3. Table of Contents

3. Table of Tables

4. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is one of the most common cancer in the world, the third most common cause of cancer-related death[1]. A majority of HCC cases (60% to 80%) arise due to chronic hepatitis and cirrhosis. Major etiologies of liver cirrhosis include chronic hepatitis B and C, alcohol consumption, steatosis, diabetes, certain medications or exposures to toxic agents and genetic and metabolic diseases[2]. Obesity has also been identified as an independent risk factor for developing HCC[3,4].

HBV is the most frequently underlying cause of HCC in Asia. HBV carriers have a 5 to 15-fold increased risk of HCC compared to the general population. Chronic HBV carriers in Asia develop HCC at an annual rate of 0.4-0.6%. In Western countries and Japan, the main risk factor is HCV infection and excessive alcohol intake, along with other causes of cirrhosis. The annual incidence rate of HCC in subjects with hepatitis C is 3.7-7.1%[5].

Various staging and classification systems have been proposed for HCC, which help to select treatment strategies, assess prognosis, and compare results from different clinical studies[6]. The Barcelona Clinic Liver Cancer (BCLC) staging system has been used for stratification of subjects with HCC in the practice guidelines established by the American Association of the Study of Liver Diseases (AASLD)[7,8]. In addition to estimating prognosis, the BCLC staging system also links staging to treatment recommendations. In this staging system, intermediate stage (BCLC-B) is formed by those subjects who are asymptomatic and harbor multifocal HCC without vascular invasion or extrahepatic spread and have preserved liver function (Child-Pugh Class A or B) and normal performance status (Eastern Cooperative Oncology Group Performance Status ECOG PS) of 0. Chemoembolization is recommended as the main treatment strategy for subjects in this intermediate stage.

Transarterial chemoembolization (TACE) is a commonly used procedure to treat liver cancers using a catheter to deliver both chemotherapy medication and embolization materials into the blood vessels that lead to the tumor. The American Cancer Society, Society of Interventional Radiology and the National Comprehensive Cancer Network have identified TACE procedures where doxorubicin (alone or mixed with other cytotoxic agents such as cisplatin and/or mitomycin C), is mixed with ethiodol and injected intra-arterially as an oily mixture into the vasculature of the tumor as the standard of care for subjects with unresectable hepatocellular carcinoma (HCC)[7].1 Following the TACE procedure, embolic particles are injected to slow the blood flow to the tumor's vasculature. This procedure is also known as conventional TACE (cTACE). Although cTACE has shown survival benefit in properly selected HCC patients from two randomized studies and a meta-analysis,[9-11] this often is associated with marked symptoms of postembolization syndrome and is not well tolerated by patients with advanced disease.[12-14]

Unlike cTACE, chemoembolization with drug-eluting beads (DEB-TACE) using doxorubicin has been found to be well tolerated with minimal postembolization syndrome

symptoms. A recent randomized study comparing cTACE and DEB-TACE has shown better tolerability and fewer complications associated with DEB-TACE[15-18].

In order to 1) minimize the loss of doxorubicin into the bloodstream; 2) prolong the residence time of doxorubicin at the tumor site; and 3) standardize TACE procedures, microsphere technology has advanced to load doxorubicin using drug eluting beads (DEB) before injection. The drug eluting bead procedure (DEB-TACE) is designed to embolize the HCC vasculature and release drug in a controlled manner. Multiple clinical trials in Europe and in the US using DEB-TACE to treat HCC have demonstrated safety, and varying degrees of success of efficacy.

5. Device Description

5.1. Device Description

Tandem Microspheres are 510(k) FDA cleared for embolization of arteriovenous malformations (AVM) and hypervascular tumors (HVT) including hepatoma. Tandem Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene®-F). They are available in a range of sizes suitable for embolic therapy. Tandem Microspheres are opaque in color.

Tandem Microspheres offer**:**

- Deep penetration into the tumor vasculature due to very small sized 40, 75, and 100 μm Microspheres.

Microspheres Diameter （μl）	Size（ml）
40	2
40	3
75	2
75	3
100	2
100	3

- High confidence when performing superselective and targeted embolization procedures as 95% of the microspheres are within the stated size variance.
- Controlled embolization with precisely formulated and standardized microspheres.
- Transcatheter arterial chemoembolization treatment with Tandem Microspheres loaded with epirubicin.

5.2. Device Labeling

STOPPER China Manuel of Operations includes Instruction for Use for Tandem

Microspheres. The labeling includes the following information:

- Product Name
- UPN
- Lot Number
- Specification (Diameters of microspheres in μm) and dosage (ml)
- Expiration Date

The labeling of products used for STOPPER China clinical trial should include the following statement:
Used for clinical trial only
The device labeling in Chinese weill be provided per China's regulatory requirement.

6. Study Objective

The primary objective of the study is to evaluate the safety and efficacy of transcatheter arterial chemoembolization with Tandem Microspheres loaded with Epirubicin in the treatment of subjects with localized hepatocellular carcinoma (HCC).

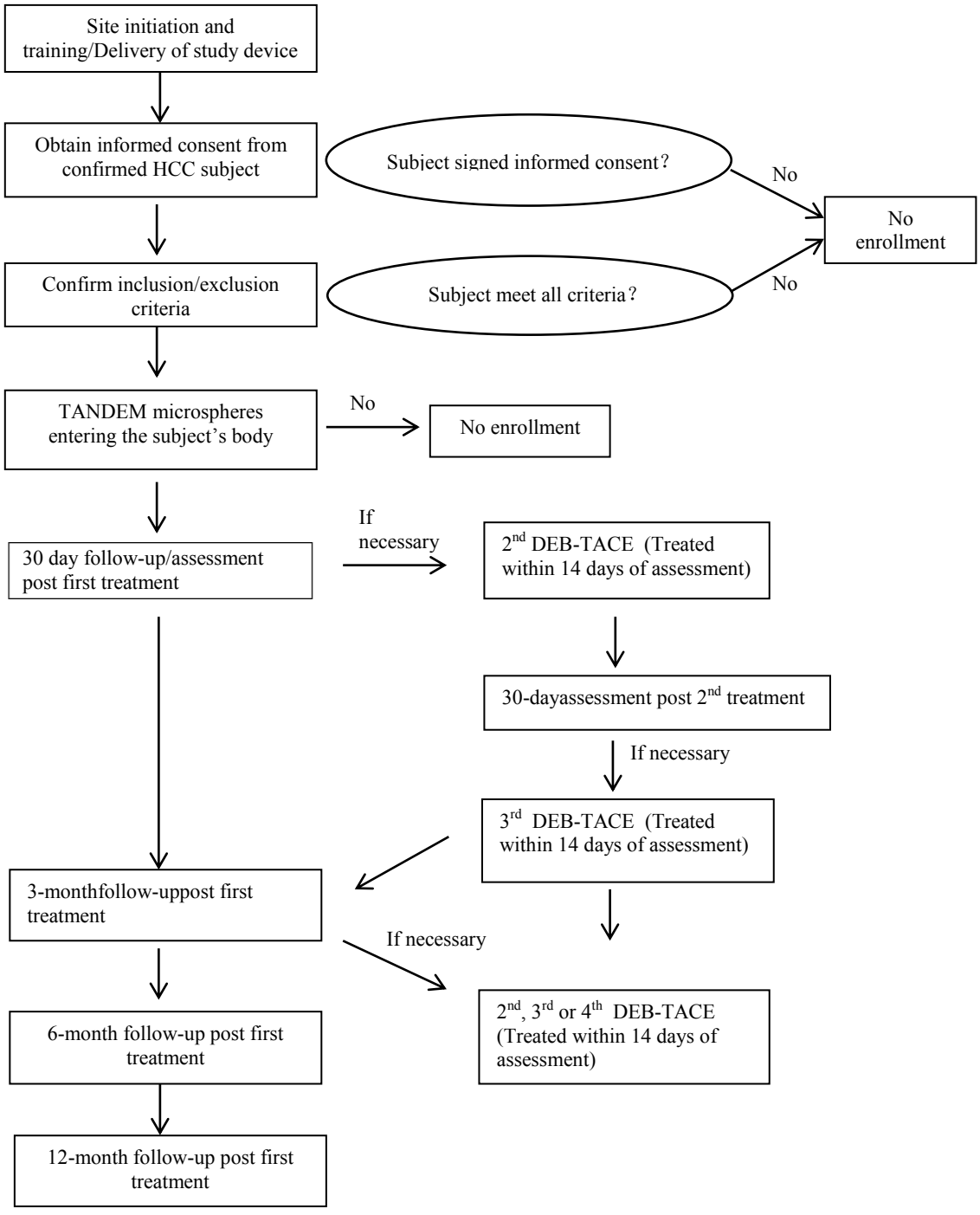
7. Study Endpoints

The primary efficacy endpoint is overall ORR at 6 months. The secondary endpoints are:

- ORR at 30 days and 3-month
- Time to Progression (TTP)
- Time to Extrahepatic Spread
- Proportion Progression-Free (PPF) at one year
- Overall survival at one year
- The frequency of treatment associated adverse events

8. Study Design

This is a prospective, single-arm, multicenter study. The flow chart of the study is as follows:


Site initiation and training/Delivery of study device
Obtain informed consent from confirmed HCC subject
Subject signed informed consent?
No
No enrollment
Confirm inclusion/exclusion criteria
Subject meet all criteria?
No
TANDEM microspheres entering the subject's body
No
No enrollment
30 day follow-up/assessment post first treatment
If necessary
2nd DEB-TACE (Treated within 14 days of assessment)
30-dayassessment post 2nd treatment
If necessary
3rd DEB-TACE (Treated within 14 days of assessment)
3-monthfollow-uppost first treatment
If necessary
2nd, 3rd or 4th DEB-TACE (Treated within 14 days of assessment)
6-month follow-up post first treatment
12-month follow-up post first treatment

8.1. Study Plan

The study will enroll 109 subjects with confirmed diagnosis of localized HCC based on the 2017 Guideline at 10 study sites. Each subject will be followed for 12 months after transcatheter arterial chemoembolization with Tandem Microspheres loaded with Epirubicin(subjects will be followed at 30-day, 3-month, 6-month and 12-month). ORR at 6 months will be assessed as the primary endpoint.

8.2. Treatment Plan

The study will consecutively enroll 109 qualified HCC subjects according to the diagnostic criteria included in the management guideline issued by China's Ministry of Health in 2017. All subjects will receive transcatheter arterial chemoembolization with Tandem Microspheres loaded with Epirubicin. Drug-loaded Tandem microspheres will be delivered into the tumor's vasculature by superselective catheter positioning. The size and specification of microspheres used in the treatment will be decided by the physician based on the tumor size and/or vascular structure. The dose of epirubicin and the volume of Tandem will be at the discretion of the physician based on the subjects's tumor situation. The treatment end point should be devascularization of tumor/lesion and delivering sufficient dose of epirubicin. If after delivering the desired drug/embolization dose, blood flow is still detectable in the tumor; then the procedure can either be stopped, or use bland Tandem microspheres to reach stasis based on the subject's condition. Prior to the procedure, the treating physician must carefully read and be familiar with the appropriate product IFU/DFU including the Loading Guidance.

<u>DEB-TACE General Procedural Considerations</u>

- Prior to the procedure, angiography of the hepatic and mesenteric arteries is performed to map the liver vascular anatomy, identify the tumor-feeding arteries and check for arteriovenous shunts.
- The goal is to deliver drug-loaded TANDEM embolic particles into the tumor's vasculature as selectively as possible. Subjects might be treated via segmental or lobar infusion if a selective or superselective approach is not feasible due to the subject's anatomy and pathology.
- Delivery of the microspheres will stop when either the total targeted microspheres have been delivered or a near stasis (slowed contrast flow for 2-5 heartbeats) endpoint has been reached.
- The doxorubicin-loaded TANDEM microspheres should be injected slowly into the tumor feeding vessels. **SLOW INJECTION IS ESSENTIAL FOR BEST RESULTS.** When flow starts to decrease, stop, wait several minutes, and then reevaluate. Flow generally will increase again and additional volume of the microspheres can be delivered as microvasculature relaxes after initial blockage.

- The goal is to saturate as much of the tumor's vascular bed as possible. The procedure is considered a technical success when the desired devascularization is achieved, or the desired dose is injected.
- If small tumor feeder arteries are missed on the first treatment, they can be addressed during a subsequent treatment.
- No embolization material other than Tandem microspheres should be used during the DEB-TACE procedure

DEB-TACE treatment can be performed for a maximum of 4 times until complete tumor response is observed on imaging or one or more of the following events occurs: Imaging assessment not indicates partial response by mRECIST after two treatments within 6 months; Development of main portal vein thrombosis or extrahepatic spread of disease; Progression to ECOG performance status $\geq$ 2 or evolution to sustained hepatic decompensation; Intolerable to treatment; Occurrence of any serious adverse event that would prompt the discontinuation of treatment. Other treatment can be initiated per investigator's discretion if no partial response is reached after two consecutive treatments. The investigator may choose adequate treatment option if new hepatic lesion or extrahepatic metastasis appears. Any anti-angiogenic drug, anti-cancer chemotherapy, immunotherapy, molecular therapy, and any investigational therapy are not allowed during the Tandem microspheres treatment. If necessary, appropriate anti-viral and/or liver protection treatments can be prescribed to chronic hepatitis patients.

8.3. Justification for the Study Design

Study has confirmed that early tumor response assessed by imaging evaluation can more accurately help to predict long-term survival in HCC patients treated with chemoembolization. Therefore, a 6-month objective tumor response rate (ORR) is used as the primary effectiveness endpoint. Since there is no report on 6-month ORR after cTACE in the Chinese population, this study selected 45% as the performance goal based on the 6-month ORR result in the cTACE controlled arm of a well-accepted international multicenter randomized controlled PRECISION V study. The PRECISION V study enrolled 212 subjects from 19 centers at France, Germany, Switzerland, Austria and Greece, The key inclusion criteria of this study is comparable with the PRECISION V study, including the BCLC staging (A/B), Child-Pugh score (A/B) and ECOG performance status (0/1).

9. Subject Selection

9.1. Study Population and Eligibility

Prior to being eligible for the STOPPER study, a subject must meet all of the inclusion criteria (Section 9.2) and none of the exclusion criteria (Section 9.3).

9.2. Inclusion Criteria

Subjects may be enrolled in the study if they meet all of the following criteria:

1. Patient is able to provide informed consent and must sign the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form.
2. Male or female of age ⩾18 and ⩽75 years.
3. Confirmed diagnosis of HCC according to the diagnostic criteria included in the management guideline issued by China's Ministry of Health in 2017.
4. HCC is diagnosed for the first time or recurrence of tumor after surgical or ablation treatment
5. Single tumor less than 7cm in diameter or multiple tumors with less than 3 lesions with >1cm in diameter, individual diameter <7cm and less than 10cm in total diameter.
6. No previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy) for HCC
7. Preserved liver function (Child-Pugh A or B7).
8. ECOG Performance Status 0 or 1.

9.3. Exclusion Criteria

Subjects will be excluded for any of the following reasons:

1. Presence of vascular invasion or extra-hepatic spread of disease, or diffuse HCC, defined as >50% liver involvement , or arteriovenuous fistula
2. Macrovascular invasion of main or primary branches of portal vein at entry into the study
3. Any contraindication for TACE treatment
4. Any contraindication for Epirubicin administration
5. Advanced liver disease (bilirubin levels >2 mg/dl, AST or ALT >5 times upper limit of normal)
6. Renal failure or insufficient renal function (Creatinine levels >2 mg/dl)
7. Subject unable to receive MRI examination
8. Pregnant or breast feeding woman, or plan to become pregnant during treatment or within 12 months of treatment
9. Couldn't commit reliable birth control measures during treatment or within 12 months of treatment
10. Subject is participating other investigational drug or device clinical trial within 30 dys of signing the informed consent
11. Subject is not suitable to participate in the study as judged by investigator

10. Subject Accountability

10.1. Enrollment

Confirmed HCC patient, who has signed the IRB/IEC-approved study ICF, and has met all inclusion criteria and none of the exclusion criteria, will be considered eligible to be enrolled in the trial. If the subject does not meet all of the inclusion criteria or meets any of the exclusion criteria, it will be regarded as screening failure, and the subject will not be enrolled in the study and receive investigational device, and will not be followed according to the study protocol. All qualified subjects will receive DEB-TACE treatment with Tandem. The enrollment timepoint will be based on subject receiving initial transcatheter arterial chemoembolization treatment with Tandem Microspheres loaded with Epirubicin

10.2. Withdrawal

All enrolled patients should be documented (including those withdraw from the study or lost to follow-up). The reason for withdrawal will be recorded in all cases of withdrawal. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to continue to follow his/her status/condition.

10.3. Enrollment Control

A minimum of 98 enrolled subjects are needed to adequately assess the primary endpoint at 6 months after initial treatment. To account for attrition, minimum enrolment shall be 109 subjects, assuming a maximum attrition of 10% for all reasons at 6 months. The enrollment cap for each study site is 25% of total enrolled subjects, which is 27 subjects. The study recruitment will stop when 109 qualified subjects completed enrollment.

11. Study Methods

11.1. Data Collection

The data collection plan is shown in Table 11.1. The follow-up window is 14 days.

Table 11.1 Baseline and Follow-up Evaluation Plan

	Screening/Baseline	Treatment initiation	30-day Follow-up post initial treatment	30-day assessment post 2nd treatment (if necessary)	3-month Follow-up post initial treatment	6-month Follow-up post initial treatment	12-month Follow-up post initial treatment
	Within 14 days of treatment	Day 0	30±14 days		91±14 days	183±14 days	365±14 days
Informed Consent	√						
Inclusion/Exclusion	√	√					
Demographics (including date of birth, gender and ethnicity)	√						
Cancer and treatment history	√						
Physical examination	√		√	√	√	√	√
Child-Pugh Score	√		√	√	√	√	√
ECG	√				√		
Laboratory tests *	√		√	√	√	√	√
Pregnancy Test # (if applicable)	√						
Imaging and tumor measurement	√		√	√	√	√	√
Chest plain CT	√		√	√	√	√	√
ECOG performance status	√		√	√	√	√	√
Concomitant Medication post treatment	√	√	√		√	√	√
Adverse Events and device failure assessment		√	√		√	√	√
Vital status			√		√	√	√

* Baseline Laboratory Tests include：complete blood count (WBC, RBC, Hb, PLT), Blood biochemistry (TP, ALB, TBIL, IBIL), Liver function tests (ALT, AST, ALP)，Renal function tests (BUN, Cr), Anticoagulation (PT, APTT, INR), Electrolyte (K, Na, CI, Ca)，hepatitis B panel and anti-HCV, AFP
# Serum and/or urine pregnant test
All laboratory tests must be completed within 14 days of study treatment，childbearing woman should complete serum and/or urine pregnant test within 7 days of treatment

11.2. Study Candidate Screening

Screening process will be performed to confirmed primary HCC subjects based on inclusion and exclusion criteria. Subjects who are suitable for DEB-TACE will be informed about the study and will be asked to sign the informed consent form (ICF) before participating in any screening procedure. After signing the ICF, the subject will receive a screening number and will be documented in a screening log. Each clinical investigator must keep a log of all screened subjects, including both eligible and non-eligible subjects (screening failures). The screening log will be kept by each study center.

11.3. Informed Consent

Before the initiation of the screening process, subjects who meet the clinical inclusion criteria will be asked to sign the IRB/IEC-approved study ICF. Subjects must be given ample time to review ICF and have questions answered before signing ICF.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, the pre-treatment tests including pre-embolization radiography may demonstrate that the subject is not a suitable candidate for the clinical trial.

11.4. Screening/Baseline Survey

The procedures to be completed within 14 days prior to treatment are as follows. Among them hepatitis B markers, HBV-DNA (if necessary), anti-HCV and imaging test result within 10 days of IC signature as well as other serum tests within 5 days of IC signature at the same research center can be accepted for screening and baseline survey data.

- Obtain written subject informed consent.
- Obtain detailed documentation of cancer history with treatments and outcomes.
- Demographics.
- Physical Examination (height, weight, pulse, blood pressure)
- Child-Pugh Score
- ECOG performance status
- Plain and Enhanced MRI to assess intrahepatic tumor
- Chest plain CT and other tests (if necessary) to exclude extrahepatic lesion
- ECG.
- Pregnancy Test: If female is of child bearing potential, non-pregnancy to be confirmed with urine or serum test.

<u>Laboratory tests to be done at baseline</u>:

- Complete Blood Count (WBC, RBC, Hb, PLT)
- Blood biochemistry (TP, ALB, TBIL, IBIL)
- Liver function tests (ALT, AST, ALP)
- Renal function tests (BUN, Cr)

- Anticoagulation (PT, APTT, INR)
- Electrolyte (K, Na, CI, Ca)
- Hepatitis B panel and anti-HCV (test HBV-DNA if HBsAg positive)
- AFP

MRI Imaging to be done at baseline and during the study treatment phase：

MRI imaging system should be ensured during all assessments for each subject with the same technique being used throughout the treatment period for evaluating the lesions. Scanning sequence include coronal T2WI，transect T2WI、T1WI、DWI，enhanced scan using 3D T1WI. Tumor measurements will be assessed at Core laboratory. Sites should send the imaging for review. The target lesions must meet all of the following according to the mRECIST for HCC Guideline：The lesion can be measured in at least one dimension ⩾ 1 cm; The lesion appears to be suitable for accurate and repeat measurement; The lesion shows intratumoral arterial enhancement。

Test to be done at baseline and during the study treatment phase to exclude extrahepatic metastasis

Perform chest CT test to exclude lung metastasis. Other tests could also be done if necessary to exclude extrahepatic metastasis.

11.5. Initial Tandem Treatment

The end of initial treatment is defined as the completion of the first DEB-TACE with Tandem microspheres. Post-treatment evaluation will be conducted by site after each DEB-TACE procedure to determine the need for next session, and complete the next embolization treatment within 14 days of assessment if necessary. A maximum of 4 treatment may be performed to the subject during the study. If a subject received 4 treatments, no 30-day post treatment assessment will be conducted, and the subject will continue to receive 6-month post treatment follow-up.See the flow chart for detailed post-treatment evaluation and follow-up plan on subjects receiving different times of DEB-TACE treatments. The following should be completed after each DEB-TACE procedure:

- Record the procedural date/time, microsphere lot #, microsphere size and volume, microcatheter used,epirubicin manufacturer, epirubicin lot #, epirubicin dose, contrast type and volume, infusion volume, lesion(s) treated and flow characteristic.
- AE and concomitant medicine used during DEB-TACE
-

11.6. 30-day Clinical Follow-up Post Initial Treatment

- Physical examination (weight, pulse, blood pressure)

- ECOG and Child-Pugh scores
- Lab tests (Complete Blood Count, blood biochemistry, liver and renal functions, blood coagulation function, electrolyte, AFP,)
- Enhanced MRI to assess the tumor response and Chest plain CT
- Concomitant medications since last visit
- Record of all adverse events that occurred from last subject contact

Note: If the 30-day evaluation post initial treatment indicates complete response of the target lesion, the subject will received scheduled 3, 6 and 12-month follow; If the 2nd treatment is needed, it will be completed within 14 days of assessment, and a 30-day evaluation will be conducted after the 2nd treatment; If the 3rd treatment is needed, it will be completed within 14 days of assessment, and the subject will receive the post-treatment evaluation and 3-month follow-up at the same time.

11.7. *3-month* (91±14 days) *Clinical Follow-up Post Initial Treatment*

- Physical examination (weight, pulse, blood pressure)
- ECOG and Child-Pugh scores
- Lab tests (Complete Blood Count, blood biochemistry, liver and renal functions, blood coagulation function, electrolyte, AFP)
- ECG
- Enhanced MRI for tumor response and Chest plain CT
- Concomitant medications since last visit
- Record of all adverse events that occurred from last subject contact

11.8. *6-month* (183±14 days) *Clinical Follow-up Post Initial Treatment*

- Physical examination (weight, pulse, blood pressure)
- ECOG and Child-Pugh scores
- Lab tests (Complete Blood Count, blood biochemistry, liver and renal functions, blood coagulation function, AFP)
- Enhanced MRI for tumor response and Chest plain CT
- Concomitant medications since last visit
- Record of all adverse events that occurred from last subject contact
- Vital status

11.9. *12-month* (365±14 天) *Clinical Follow-up Post Initial Treatment*

- Physical examination
- ECOG and Child-Pugh scores

- Lab tests (Complete Blood Count, blood coagulation function, AFP, liver and renal functions)
- Enhanced MRI for tumor response and Chest plain CT
- Concomitant medications since last visit
- Record of all adverse events that occurred from last subject contact
- Vital status

11.10. Study Completion

All subjects who completed the 12 months follow-up, or withdrawn (due to death or loss to follow-up), or will be treated as study termination. Any adverse events occurred afterwards will be addressed by the physician per standard treatment.

Subjects may withdraw their consent and discontinue participation in the clinical study at any time, for any reason, without prejudice to further treatment. If a subject no longer wants to receive study treatment, but is willing to come for follow-up appointments, the subject's request should be honored, if possible.

If for any reason a subject is withdrawn or terminated before completing the study, the reasons for withdrawal or termination must be documented.

If a subject discontinues treatment due to an adverse event or clinical laboratory abnormality, the subject should be followed-up until the event resolves or the subject stabilized.

12. Statistical Considerations

12.1. Endpoints

12.1.1. Primary Endpoint

The primary endpoint of the study is 6-month ORR. Objective tumor response will be assessed by The European Association for the Study of the Liver (EASL) Response Evaluation Criteria in Solid Tumors and a modified Response Evaluation Criteria in Solid Tumors (mRECIST[19]). The mRECIST criteria can be more accurate to predict long-term survival in HCC subjects treated with chemoembolization[20]. The subject achieves complete response (CR) or partial response (PR) will be regarded as a responder. A subject without tumor assessment after the initiation of the treatment will be regarded as a missing data.

12.1.1.1. Hypotheses

The primary hypotheses is the 6-month ORR in subjects treated with transcatheter arterial chemoembolization with drug-loaded Tandem Microspheres exceeds the PG under a one-sided significance level of 2.5%. The PG development is based on PRECISION V, an international multicenter study. The ORR will be assessed based on the EASL criteria.

The null (H_0) and the alternative (H_1) hypotheses for the primary effectiveness endpoint are as follows:

H_0: $P_e \leq PG$ (not met)

H_1: $P_e > PG$ (met)

where P_e is the expected 6-month ORR (%).

12.1.1.2. Sample Size

The overall sample size is driven by the primary effectiveness endpoint. Approximately 109 subjects are planned to be enrolled in the study. The sample size justification is based on the following assumptions.

- Power ⩾ 85%
- One-sided significance level = 2.5% (alpha)
- PG for 6-month ORR = 45%
- Expected 6-month ORR = 60%
- A minimum of 98 evaluable subjects are required for 6-month assessment
- Attrition rate = 10% (loss to follow-up in 6 months)
- A sample size of 109 subjects will be enrolled in the study

12.1.1.3. Statistical Methods

A normal approximation test (e.g. Chi-Square Test) will be used to assess the superiority to the PG.

12.1.1.4. Success Criteria

The test device will be concluded to be superior to the PG if the one-sided 97.5% lower confidence bound for the observed performance in 6-month ORR is greater than PG.

12.1.2. Secondary Endpoints

The study is not powered for the secondary endpoints therefore there are no formal hypotheses. The secondary endpoints and analyses are shown below.

Kaplan-Meier analyses will be used for time-to-event type of endpoints such as overall survival (OS), time to progression (TTP), and time to extrahepatic spread through 12 months. A binary proportion will be presented for ORR at 30-day and 3-month and progression-free (PPF) rate at 12 months. A frequency will be provided for treatment associated adverse events.

12.2. General Statistical Considerations

12.2.1. Analysis Sets

The primary and pre-specified secondary endpoints will be analyzed on a Per Protocol and as treated basis. Only enrolled subjects who receive the first treatment will be included in the analysis sample.

12.2.2. Control of Systematic Errors/Bias

Selection of subjects will be made from the Investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria and that have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the trial to minimize selection bias. the MRI core laboratory will independently analyze the images and the data obtained from the core laboratory will be utilized for analyses.

12.2.3. Number of Subjects per Investigative Site

Each site will be allowed to enroll up to 25% of the total enrollment, with a maximum enrollment of 27 subjects.

12.3. Baseline Data Analysis

Baseline demographics, procedure and assessments will be summarized for the study. For continuous and/or ordinal variables, the descriptive statistics will include mean, standard deviation, number evaluated, minimum and maximum. Some specific variables may also include additional statistics such as median and confidence intervals. For binary or categorical variables, the descriptive statistics will include percentage, numerator, denominator, and number evaluated. Some variables may include confidence intervals as needed.

12.3.1. Other Endpoints/Measurements

Other assessments including ad-hoc analyses will be observational only.

12.3.2. Subgroup Analysis

The primary endpoint and/or additional assessments may be summarized by the following categories as applicable:

- Gender (male vs. female)
- ECOG Score (0 vs. 1)
- BCLC Stage (A vs. B7)

12.3.3. Sensitivity Analysis for Missing Outcome Data

Sensitivity analysis for the primary endpoint assessment will be conducted to assess the impact of missing data on the result's robustness. In addition to the use of the worst-case analysis, the tipping point analysis will be performed for the ITT analysis set to consider all combinations of present/absent for all subjects with missing primary outcome.

12.3.4. Multivariable Analyses

Univariate and multivariable analyses may be performed as post-hoc analyses to assess the effect of potential predictors for the primary endpoint in a logistic regression model.

Clinically and/or statistical meaningful baseline covariates will be selected in the regression model if the analysis is performed.

12.3.5. Analysis Software

All statistical analyses will be performed using the Statistical Analysis Software (SAS), version 9.2 or later (Copyright © 2002-2010 by SAS Institute Inc., Cary, North Carolina 27513, USA. All rights reserved)

12.3.6. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the primary analyses will be documented in an amended Statistical Analysis Plan prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical trial report along with a reason for the deviation.

13. Data Management

13.1. Data Collection, Processing, and Review

Subject data will be recorded in a secure electronic data capture (EDC) system. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server provided by Medidata. All changes made to the clinical data can be tracked and available for review by BSC or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

Each study subject will be assured of signing the informed consent before participating in the study. Any missed follow-up, missed trial, missed test and correction of error and missing data will be clearly and faithfully recorded.

13.2. Data Retention

The Principal Investigator or his/her designee will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects. Documents must be retained for 10 years after the formal discontinuation of the clinical investigation of the product. These documents will be retained by BSC until the product/device is no longer in use in compliance with local regulations.

BSC will notify investigators and study sites the retention time of the documents. The investigators and study sites will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigators and study sites withdraw responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. Core Laboratory

The STOPPER China clinical trial will use a Core Laboratory to conduct independent data analysis. See the Manuel of Operations for operating guide on data collection, analysis and interpretation.

The independent Core Laboratory will assess the tumor response using EASL and mRECIST criteria (at baseline, 30-day, 3-month, 6-month and 12-month post initial treatment) based on the plain scan and enhanced MRI imaging performed for subjects enrolled at respective study sites.

14. Protocol Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IEC/CFDA) of the revised protocol must be obtained prior to implementation.

15. Protocol Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the Sponsor and the reviewing IEC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor using the EDC CRF. Centers may also be required to report deviations to the IEC, per local guidelines and government regulations.

All protocol deviations (PDs) are classified as "major" or "minor" as defined below:

- A major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), OR a protocol deviation that compromises the safety and welfare of study participants.
- A minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), AND does not compromise the safety and welfare of study participants.

The sponsor should ensure all investigators participating in the clinical trial will strictly follow the study protocol, and should notify and correct any non-compliance activity to relevant law and regulations, China Medical Device GCP and study protocol conducted by the study site and investigator. The sponsor should terminate the study if the violation is serious or continue, and report to provincial and city food and drug supervision and administration department and CFDA.

16. Device Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. The investigational medical device should be properly labeled as "Investigational use". The sponsor shall keep records to document the physical location of all investigational Tandem microspheres from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date
- Date or dates of use
- Subject identification
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable. Written documents are required per country regulation

17. Compliance

17.1. Statement of Compliance

This study will be conducted in accordance with ISO 14155:2011 (2nd Edition; 2011-02-01) Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of

Helsinki, and pertinent China's laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/IEC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/IEC or regulatory authority shall be followed, if appropriate.

17.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155 or ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IEC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency; and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements.
- Report all SAEs and device deficiencies that could have led to a SAE and potential/USADE or UADE to BSC by written documents, per the protocol requirements.
- Report to the IEC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IEC, and supply BSC with any additional requested

information related to the safety reporting of a particular event; provide all required source documents related to a death event to BSC and the IEC per local requirements. Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.

- Allow the Sponsor and Sponsor representatives to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IEC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IEC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator (including but not limited to conducting the informed consent process), the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The

investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. Institutional Review Board/ Ethics Committee

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment.

Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

17.4. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.5. Insurance

BSC will obtain insurance coverage for subjects in the study as per China's regulatory requirement. In case the study related injury occurs, the study site will be responsible for the claim process in accordance with the relevant insurance process, and BSC will assume corresponding responsibilities according to the insurance clause, except that the injury is due to protocol violation or intended/serious negligence by study site.

18. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the approved protocol/modifications and applicable regulations. In addition, the clinical research monitor will verify the informed consent of all enrolled participants at study sites, study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The monitoring frequency will be increased and/or relevant corrective measures will be conducted if protocol violation and compliance exceeded the pre-specified setting. For this study, the source document includes at least, but not limited to: signed informed consent (ICF), subject's original medical records, imaging results (if any), laboratory results, SAEs report and device inventory form. The device deficiencies recorded on the CRF, the relationship between AE and study device, and procedure and ADE prediction assessment related data can be regarded as the study's source data

The Principal Investigator/institution guarantees direct access to original digital or paper source documents (digital source document refers to the scanned document with physician's signature conformation, paper source document refers to traditional handwriting medical record) by BSC personnel, their designees, and appropriate regulatory authorities. The copy of the source medical record must be verified if the original source medical record is unavailable due to subject's visiting to the non-study site and non-study investigator. As described in Section 20, SAE related original record (from study site or non-study hospital if applicable) should be obtained and forwarded to BSC's safety affairs office.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1. Anticipated Adverse Events

The following anticipated adverse events (AE) have been identified for this study：

1. Vascular embolization is a high risk procedure. The procedure should be performed by specialized physicians trained in vascular embolization procedures. Complications can occur at any time during or after the procedure, and may include, but not limited to:

Table 19.1-1：Potential complications and incidence rates

Potential complication	Incidence rates
Post-embolization syndrome	24.7%
Liver abscess	2.3-7.4%
Liver failure	1.2-4.6%
Cholecystitis	0.9-5.4%

Pancreatitis	0.9-3.8%
Renal complication	1.3-2.8%
Hypertension	5%
Myocardial infarction	0.3-2.2%
Vascular complication(include vessel injury and incision hematoma)	2.4 -3%
Non-target embolization	1.8%
Pulmonary embolism	0.6-1.8%
Pleural effussion	4%
Infection	0.9-6%
Death	0-2.4%

* Definition of the post-embolization syndrome: symptoms of nausea, vomiting, local pain, fever, reflex intestinal distention or paralytic ileus and loss of appetite due to ischemic necrosis post tumor and organ embolization.

2. Drug related adverse events observed in the clinical trials of epirubicin include (but not limited to):

- Infection and infestation：infection
- Benign and malignant tumor：acute lymphocytic leukemia，acute myeloid leukemia
- Abnormal blood and lymphatic system：anemia、thrombopenia、febrile neutropenia、neutropenia、leucopenia
- Metabolic and nutritional abnormalities：anorexia
- Eye abnormalities：conjunctivitis/keratitis
- Abnormal cardiac function：congestive heart failure、ventricular tachycardia、atrioventricular block、bundle branch block、bradycardia
- Vascular anomaly：hot flashes、thrombus
- Gastrointestinal tract abnormalities：nausea/vomiting、mucositis/stomatitis、diarrhea
- Abnormal skin and subcutaneous tissue：alopecia、local toxicity、rash/itching、skin changes
- Reproductive system and breast abnormalities：amenorrhoea
- Abnormal systemic and drug delivery site：discomfort/fatigue、fever
- Exam：asymptomatic left ventricular ejection fraction reduction，changes in the level of aminotransferase

19.2. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

19.3. Anticipated Benefits

Transcatheter Arterial Chemoembolization (TACE) is expected to improve the survival in localized HCC patients. The patient's health and medical status will be closely monitored, and may benefit from the tests that are performed as part of the study. The data resulting from participation may be of a great value and help physicians and future patients.

19.4. Benefit-Risk Ratio

The Tandem microspheres will only be used for anticipated IFU. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate Directions for Use (DFU). Evaluation of the risks and benefits that are expected to be associated with use of the Tandem microspheres demonstrate that when used under the conditions intended, the benefits associated with use of the Tandem microspheres should outweigh the risks.

20. Safety Reporting

20.1. Events reported by investigator to sponsor

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. For centers in Austria cancer must always be reported as a Serious Adverse Event. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

20.2. Definitions and Classification

Safety definitions are provided in Table 20.2-1 with reference from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 20.2-1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011*	Adverse event that: Led to death, Led to serious deterioration in the health of the subject, that either resulted in: a life-threatening illness or injury, or a permanent impairment of a body structure or a body function,

Table 20.2-1: Safety Reporting Definitions

Term	Definition
	or in-patient hospitalization or prolongation of existing hospitalization of existing hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function Led to fetal distress, fetal death, or a congenital abnormality or birth defect. NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011*	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. NOTE 1: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if

Table 20.2-1: Safety Reporting Definitions

Term	Definition
	intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol.

20.3. Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device, epirubicin or procedure. See criteria in Table 20.3-1

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device

Classification	Description
	belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

20.4. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 20.4-1.

Table 20.4-1: Investigator Reporting Requirement

Event Classification	Communication Method	Communication Timeline pre-market studies*
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Terminating at the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Reporting required through the end of the study

Event Classification	**Communication Method**	**Communication Timeline pre-market studies***
	Provide all relevant source documentation (unidentified) for reported event	When source document is available.
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	When source document is available.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete device malfunction page with all available new and updated information.	• Within 24 hours of first becoming aware of the event. • Reporting required through the end of the study
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner but no later than 10 business days after becoming aware of the information • • Reporting required through the end of the study.

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

20.5. Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in Device Management Plan. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) should not be reported as AEs. Instead, they should be reported on the appropriate eCRF. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

Device deficiencies that did not lead to an AE but could have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) circumstances had been less fortunate must be reported as described in Table 20.4-1.

20.6. Reporting to Regulatory Authorities/IRBs/ECs/ Investigators

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/ECs in a timely manner.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection (except any screening tests waived in the protocol).

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki; the relevant parts of ISO 14155: 2011 and the ICH guidelines for GCP; any applicable national regulations; and local Ethics Committee and/or

Regulatory authority body, as applicable. The ICF must be approved by the site's IEC, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IEC. Any modification requires acceptance from BSC or authorized representative prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IEC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g. IEC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following

annual review by the IEC. The new version of the ICF must be approved by the IEC. Acceptance by Boston Scientific Corporation is required if changes to the revised ICF are requested by the site's IEC. The IEC will determine the subject population to be re-consented.

22. Committee

22.1. Executive Committee

An Executive Committee composed of BSC Clinical Management, study Principal Investigator will be convened. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, overall data quality and integrity, and timely dissemination of study results through appropriate scientific sessions and publications. As appropriate the Executive Committee may request participation of STOPPER CHINA Investigators on the Committee.

22.2. Safety Monitoring Process

To promote early detection of safety issues, the BSC Safety team and its delegated CRO Safety team will provide review, process, monitor and evaluation of the safety events defined in the study-specific safety plan. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23. Suspension or Termination

23.1. Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- Important new information affecting continuation of the study (Such as safety and device performance)
- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- A decision on the regulatory authority to terminate this study early.

- A decision on the part of Boston Scientific to suspend or discontinue development of the device.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

Note： According to protocol requirement listed in Section 20, the assessment and report of AE、SAE、SADE and device deficiencies in subjects receiving study devices need to be continued even if the study has been terminated.

23.2. Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or IRB/ EC in the STOPPER Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3. Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4. Criteria for Suspending/Terminating a Study Site

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed for 12

months. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

According to Section 20, all study participants who have received study device treatment will need continuous adverse events assessment and report. The principal investigators at study sites need to continue the follow-up unless being notified by Boston Scientific.

24. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

25. Reimbursement and Compensation for Subjects

25.1. Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

25.2. Compensation for Subject's Health Injury

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, and if required by applicable law.

26. Literature

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27. Abbreviations and Definitions

See Table 27.1 for Abbreviations.

Table 27.1 Terms and Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase, Serum glutamic pyruvic transaminase (SGPT)
AST	Asparagine aminotransferase, Serum glutamic oxaloacetic transaminase (SGOT)
AVM	Arteriovenous malformation
BCLC	Barcelona Clinical Liver Cancer staging
CBC	Complete Blood Count
CR	Complete Response
CRO	Contract Research Organization
cTACE	Conventional transarterial chemoembolization
CRF	Case Report Form
DEB-TACE	Drug eluting bead-transarterial chemoembolization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practices
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
ICH-GCP	International Conference on Harmonization-Good Clinical Practices
IDE	Investigational Device Exemption
INR	International normalized ratio
IRB	Institutional Review Board
IRRP	Independent Response Review Panel
ISO	International Standards
ITT	Intent-to-Treat
mRECIST	Modified RECIST
MRI	Magnetic Resonance Imaging
PD	Progressive Disease
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
TACE	Transarterial chemoembolization
TTP	Time to Disease Progression
UADE	Unanticipated Adverse Device Effect

See Tables 27.2 for Definitions

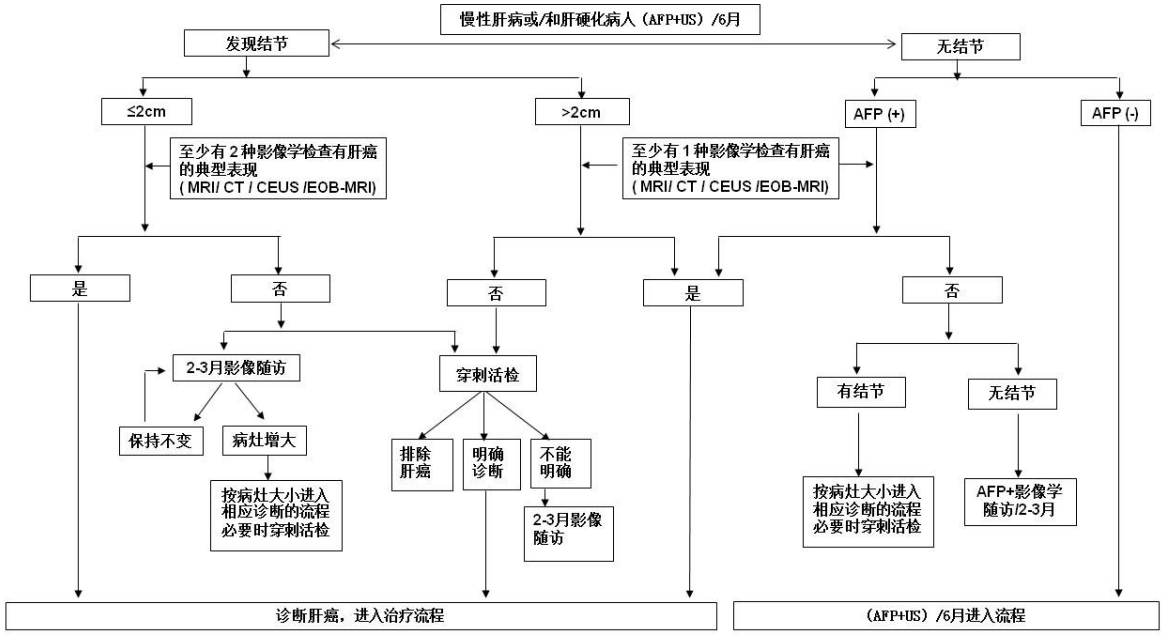
Table 27.2: Definitions

Term	Definition
BCLC Staging System	The Barcelona Clinic Liver Cancer Staging System is a well-accepted system that uses tumor stage, liver function, physical status, and cancer related symptoms, to classify the stages with a treatment algorithm.[4]
Child-Pugh Score	The Child-Pugh score is a measure of liver function. [4] It is calculated from the sum of the points for each Child Pugh Classification (CPC) criteria. See Appendix B
ECOG Performance Status	An Eastern Cooperative Oncology Group (ECOG) assessment of performance status describes a patient's level of functioning in terms of their ability to care for them self, daily activity, and physical ability (walking, working, etc.). See Appendix A.
Investigational Device	Boston Scientific Corporation ONCOZENE™ or TANDEM™ Microspheres loaded with doxorubicin
mRECIST Criteria	A post-treatment assessment of tumor response by magnetic resonance imaging (MRI) scan. See Appendix C.
Near-Stasis	A degree of stasis where near complete loss of intra-tumoral vascularity is shown by a slowed contrast flow for 2-5 heartbeats.
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.
Target Tumor	The lesion can be measured in at least one dimension $\geqslant$ 1 cm; The lesion appears to be suitable for accurate and repeat measurement; The lesion shows intratumoral arterial enhancement

Attachment A: Diagnostic criteria included in the management guideline issued by China's Ministry of Health in 2017

1. Subject diagnosed as hepatitis B or C, or liver cirrhosis of any cause should receive ultrasound and AFP test at least every 6 months. The clinical diagnosis of HCC can be made if the intrahepatic nodule of ≤2cm in diameter is identified and at least two of the following four tests indicate the typical "fast in and fast out" HCC characteristics with significant enhancement of lesion in the arterial phase and reduced enhancement of portal vein or delayed phase: dynamic enhancement MRI, dynamic enhancement CT, contrast-enhanced ultrasonography and Primovist dynamic enhancement MRI. For intrahepatic nodule of >2cm in diameter, the clinical diagnosis of HCC can be made if one of the four tests indicate the typical HCC characteristics.

2. Subject diagnosed as hepatitis B or C, or liver cirrhosis of any cause: HCC diagnosis can be confirmed with liver biopsy or close imaging follow-up if the intrahepatic nodule is ≤ 2cm in diameter and only one of the above four imaging tests indicate typical HCC characteristics; For intrahepatic nodule >2cm in diameter and no typical HCC characteristics by any of the four tests, the diagnosis should be confirmed by liver biopsy.



Appendix B: ECOG Performance Status

Performance Status Criteria:
ECOG and Karnofsky Performance Scores

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix C: Child-Pugh Score

		1 point	2 points	3 points
Serum Bilirubin	mg/dL	<2	2-3	>3
	μmol/L	<34.2	34.2-51.3	>51.3
Serum Albumin	g/dL	>3.5	2.8-3.5	<2.8
	g/L	>35	28-35	<28
INR		<1.7	1.7-2.30	>2.30
Ascites		None	Mild	Severe
Hepatic encephalopathy		None	Grade I-II	Grade III-IV

Class A: 5-6 points, Class B: 7-9 points, Class C: 10-15 points

Appendix D：mRECIST Response Assessment of Target Lesion for HCC

Target Lesions	
Response Category	mRECIST
CR	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as a reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Appendix E： EASL Response Assessment of target lesion for HCC

Response Category	EASL Criteria
Complete Response (CR)	Disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart
Partial Response (PR)	At least 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart
Stable Disease (SD)	Any cases that do not qualify for either PR or PD
Disease Progression (PD)	At least 25% increase in size of one or more measurable lesions or the appearance of new lesions