FFCD 1307

CHEMOEMBOLIZATION OF S HEPATOCELLULAR CARCINOMAS NOT UNDERGOING CURATIVE TREATMENT, USING IDARUBICIN-LOADED BEADS

IDASPHERE II

Phase II: single arm - multicenter

Eudract number: 2014-000050-10

COORDINATOR :
Dr Boris GUIU
Saint-Eloi University Hospital
Department of Radiology
80 Augustin Fliche Avenue
34295 Montpellier
Tel : 04 67 33 75 40- Fax : 04 67 33 75 49
Email: b-guiu@chu-montpellier.fr

CO-COORDINATOR:
Dr Jean-Claude BARBARE
CHU Hôpital Nord2
Place Victor Pauchet - BP 300680054
AMIENS
Tel : 03 22 66 80 60 - Fax : 03 22 66 87 52Email : Barbare.Jeanclaude@chu-amiens.fr

CO-COORDINATOR representing the AFEF group:
Pr Philippe MERLE
CHU de Lyon - Croix
RousseHGE Department
- CCC103
Grande Rue de la Croix Rousse69317
LYON
Tel : 04 72 41 30 84 - Fax : 04 72 41 31 40
Email: philippe.merle@inserm.fr

Protocol Writing Committee:
Eric Assenat (Montpellier), Thierry de Baère (Villejuif), Jean-Claude Barbare (Amiens), Laurent Bedenne (Dijon), Mathieu Boulin (Dijon), Christelle de La Fouchardière (Lyon), Alban Denys (Lausanne), Boris Guiu (Dijon), Karine Le Malicot (FFCD), Philippe Merle (Lyon), Marie Moreau (FFCD), Jean-Louis Legoux (Orléans), Jean-Louis Jouve (Dijon)

PROMOTER AND CENTRE DE RANDOMISATION -GESTION-ANALYSE (CRGA): Faculté de Médecine, 7 Boulevard Jeanne d'Arc, BP 87900, 21079 Dijon Cedex, France

Francophone Federation of Digestive Oncology (FFCD) : **Cécile GIRAULT- Administrative Director**
Tel: 03 80 66 80 13 - Fax: 03 80 38 18 41
E-mail: cecile.girault@u-bourgogne.fr

Statistician : **Emilie MAILLARD**
Tel: 03 80 39 34 71- Fax: 03 80 38 18 41

E-mail: emilie.maillard@u-bourgogne.fr

mailto:

Project manager: **Marie MOREAU**
Tel: 03 80 39 34 04- Fax: 03 80 38 18 41
E-mail : marie.moreau@u-bourgogne.fr

SUMMARY

CONTACTS FFCD

Randomization + EIG declaration : Fax : 03 80 38 18 41 - Tel : 03 80 66 80 13

NAME	FUNCTION	PHONE	TELECOPIE	E-MAIL
ADMINISTRATIVE MANAGEMENT				
Cécile GIRAULT	Administrative Director	03 80 39 33 87	03 80 38 18 41	cecile.girault@u-bourgogne.fr
Martina SCHNEIDER	Assistant Administrative Director	03 80 39 34 83	03 80 38 18 41	martina.schneider@u-bourgogne.fr
Aurélie DUBREU	Executive secretary	03 80 38 13 14	03 80 39 34 85	Aurelie.Dubreu@u-bourgogne.fr
RANDOMIZATION CENTER - MANAGEMENT - ANALYSIS				
Karine LE MALICOT	Statistician	03 80 39 34 71	03 80 38 18 41	karine.le-malicot@u-bourgogne.fr
Emilie MAILLARD	Statistician	03 80 39 34 81	03 80 38 18 41	emilie.maillard@u-bourgogne.fr
Fadil MASSKOURI	Data Manager	03 80 39 34 05	03 80 38 18 41	fadil.masskouri@u-bourgogne.fr
Carole MONTERYMARD	Data Manager/Stat	03 80 39 34 84	03 80 38 18 41	carole.monterymard@u-bourgogne.fr
Charles FUCHEY	Data Manager	03 80 39 34 53	03 80 38 18 41	Charles.Fuchey@u-bourgogne.fr
Paolo CARNI	Data Manager/Stat	03 80 39 34 53	03 80 38 18 41	paolo.carni@u-bourgogne.fr
Mickael VOYE	Assistant Data Manager	03 80 66 80 13	03 80 18 41	mickael.voye@u-bourgogne.fr
Marie MOREAU	Project Manager	03 80 39 34 04	03 80 38 18 41	marie.moreau@u-bourgogne.fr
Jaïque CARIO	Assistant Project Manager	03 80 39 34 86	03 80 38 18 41	jcario@u-bourgogne.fr
Géraldine VAUDRIT	Assistant Project Manager	03 80 39 33 86	03 80 38 18 41	Geraldine.Vaudrit@u-bourgogne.fr
Gaëlle DELIGNETTE	Assistant Project Manager	03 80 39 34 86	03 80 38 18 41	Gaelle.Delignette@u-bourgogne.fr
Caroline CHOINE-POURRET	ARC coordinator	04 69 18 19 02	09 74 44 22 47	carolinechoine.ffcd@sfr.fr
FFCD ARC Team				
Florence GUILIANI-KPODOH	Hicham FATTOUH	Nicolas LE PROVOST	Guillaume ARNOULD	E-mail and telephone contact information in the investigator's binder
Nouredine LASMI	Huguette MATENE	Morgane MAURY-NEGRE		

You can also contact the CRGA of the FFCD at: 03 80 66 80 13 (Monday to Friday from 9H00 to 18H00)

PROTOCOL AGREEMENT AND BPC

FFCD 1307
Chemoembolization of hepatocellular carcinoma not amenable to curative treatment with idarubicin-loaded beads - IDASPHERE II
PHASE II: Single-armed, multi-center

Eudract No. 2014-000050-10

Version 2.1 - 8.10.2014 containing amendment 1

This version of the protocol is approved by :

The Promoter : Ms. Cecile GIRAULT Date: 21/01/2014Signature :

The Coordinator: Dr Boris GUIU Date: 01/21/2014Signature:

I, the undersigned, Doctor : .....
.....
After having read the requirements of this research, the protocol and its annexes, I hereby certify that I will conduct this trial in compliance with Good Clinical Practices and in accordance with the applicable provisions of the Public Health Code.

In particular, I agree to:

- to respect the protocol as well as all modifications notified to me by the Promoter
- agree to supervise the research in the center and to train my collaborators in the conduct of the research and provide a list of their names
- Have each patient sign a written consent after having read the information note intended for them
- Report serious adverse events or developments within 24 hours of learning of them, and as specified in the research protocol
- respect the inclusion and non-inclusion criteria, as well as the start and end dates of the study
- send copies of evaluation reports as recommended,
- complete all the items in the observation book, ensure the quality of the data collection and the proper management of the products
- retain research data and documents until notified by the Sponsor that it is no longer required
- inform the Sponsor of any conflict of interest situation that may affect my scientific independence in the context of the research
- inform the Promoter without delay of any action, whether amicable or contentious, brought by a person involved in the research or his or her beneficiaries, which could call into question the responsibility of the Promoter
- accept periodic visits by the Sponsor's representatives, and make available to them all source documents and materials related to the research in order to ensure quality control of the data recorded in the case report book. I agree to be audited by the Sponsor and/or inspected by the health authorities
- respond by phone or mail to requests for corrections or clarifications regarding the observation book
- Allow time for the ARC FFCD to sign the forms, answer any questions and take action

Date: Signature:

STAMP of the CENTER :

Send the original to the CRGA of the FFCD - 7 bd Jeanne d'Arc - BP 87900 - 21079 Dijon Cedex

LIST OF ABBREVIATIONS

ACE	embryonic carcino antigen
AFP	Alpha-fetoprotein
ALAT	Alanine aminotransferase (or SGPT: serum glutamic pyruvic transaminase)
ANSM	National Agency for the Safety of Medicines and Health Products
ARC	Clinical Research Associate
ASAT	Aspartate-aminotransferase (or SGOT: serum glutamic oxaloacetic transaminase)
VKAS	Anti Vitamin K
CCRm	Metastatic colorectal cancer
CHC	Hepatocellular carcinoma
CHE	CHimioEmbolization
PPC	Committee for the Protection of Persons
CNHIM	National Hospital Drug Information Center
CRF	Case Report Form
CTC	Common Toxicity Criteria
CVIR	CardioVascular and Interventional Radiology
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EI	Adverse event
ISG	Serious adverse event
5FU	5-fluorouracil
FFCD	French-speaking Federation of Digestive Oncology
FOLFIRI	Fluorouracil - folinic acid - irinotecan
GGT	Gamma glutamyl transpeptidase
Hb	Hemoglobin
HR	"Hazard ratio
HTA	Hypertension
INR	International Normalized Ratio
MRI	Magnetic resonance imaging
ITT	Intent to treat
IV	Intravenous
j	Day
KM	Kaplan Meyer
LDH	Lactate dehydrogenase
LSN	Upper limit of normal
N	Normal
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NFS	Blood count
WHO	World Health Organization
PAL	Alkaline phosphatases
PA	Blood pressure
PAD	Diastolic blood pressure
NOT	Systolic blood pressure
PG	Progastrin
Q1-Q3	Quartiles
RECIST	Response Evaluation Criteria In Solid Tumors
RC	Full Answer
RP	Partial response
PNN	Neutrophils
SG	Overall survival
SD	Stability
TAP	Thoracic-Abdomino-Pelvic
CT	CT scan
TP	Prothrombin level
UICC	International Union Against Cancer
VEGF	Vascular endothelial growth factor

SYNOPSIS

Essay title:	**Chemoembolization of hepatocellular carcinoma not amenable to curative treatment with idarubicin-loaded beads - IDASPHERE II** **PHASE II: single arm - multicenter**
Trial number	FFCD 1307
Developer	French-speaking Federation of Digestive Oncology (FFCD)
Coordinator	Dr Boris GUIU
Co-coordinators	Dr Jean Claude BARBARE (FFCD), Pr Philippe MERLE (AFEF)
Participating groups	FFCD-AFEF
Rationale for the study	The products most used in HEC are doxorubicin (36%), cisplatin (31%) and epirubicin (12%) [Marelli et al. CVIR 2007]. Until recently there was no clear rationale for choosing one product over another. Indeed, systemic chemotherapy is considered ineffective in HCC [Burrough, Lancet Oncol 2004], which does not provide an argument for the choice of product. In addition, 2 randomized trials designed to compare molecules (doxorubicin versus epirubicin) were negative in terms of survival [Kawai, Sem Oncol 1997; Watanabe, Cancer Chemoth Pharm 1994]. A study conducted at the University Hospital of Dijon, tested the cytotoxicity of various anticancer agents on HCC cell lines, with the aim of selecting the best candidate for HEC (Boulin et al., Anticancer drugs 2011). Eleven chemotherapy molecules, including those most frequently used for HEC, were tested. Among them, idarubicin (an anthracycline) was by far the most effective in vitro. The superiority of idarubicin (over doxorubicin) was observed especially in the SNU-449 line, which is known to be resistant to several chemotherapeutic agents [Park, JNCI 1994]. Two mechanisms may explain this better cytotoxicity: 1) idarubicin has a better intracellular penetration than other anthracyclines [Broggini, Cancer Treat Rep 1984]. This is probably due to its greater lipophilicity, facilitating its passage through the membrane composed of a double lipid layer, 2) idarubicin resists the multidrug resistance (MDR) system [Roovers, Leuk Res 1999]. The MDR mechanism, often observed in HCC, consists of membrane pumps that transport the molecule out of the cell. These two particularities could explain a higher accumulation of idarubicin in HCC cells and thus a better efficacy. It is interesting to note that idarubicin administered orally (5mg/day for 21 days) has been shown to have low toxicity and efficacy in HCC [Tumolo, ASCO 2002]. Currently, idarubicin is used to treat leukemia. Its toxicity profile (in particular hematological and cardiac) is known. Based on these findings, a pilot study was conducted to evaluate the safety and efficacy of lipiodol-based HEC using a dose of 10 mg idarubicin in 21 patients with unresectable HCC. These preliminary data show that HEC with idarubicin is effective and has low toxicity (Favelier et al., CVIR 2013). As idarubicin can be loaded on microbeads, a phase I study (IDASPHERE I) (submitted article Clin Cancer Research) with DC Beads® (300-500µm) loaded with idarubicin (dose escalation from 5 to 25 mg) was conducted at the Dijon University Hospital. DLT and MTD were determined in 21 patients using a CRM (Continual Reassessment Method). The MTD of idarubicin was evaluated at 10mg. The idarubicin-loaded beads did not pose any specific toxicity concerns. The 10mg dose is consistent with the known toxicity profile of idarubicin: cumulative cardiotoxicity of doxorubicin is observed from 550mg/m², while that of idarubicin is observed from 93mg/m². There is thus a 5.9:1 ratio between their cumulative toxicities. The most commonly used (and lowest) dose for doxorubicin-based HEC is 50 mg. The dose equivalent of idarubicin would therefore be: 50 mg (doxorubicin) / 5.9 (doxorubicin/idarubicin ratio) = approximately 10 mg of idarubicin. The hepatic extraction of idarubicin has already been shown to be better than that of doxorubicin and daunorubicin in an animal model of sarcoma. In this study, the AUC 0-48h and AUC 0-72h were 1.35 times higher with idarubicin, showing that its intrahepatic penetration was 35% higher [Broggini M et al. Cancer Treat Rep 1984]. The PRECISION V randomized phase II trial compared conventional HEC (cCHE) with doxorubicin-loaded bead HEC (DC Bead®) in patients with HCC (Lammer et al. Cardiovasc Intervent Radiol. 2010). This is currently the only published randomized trial comparing the effect of conventional HEC (cCHE) with doxorubicin-loaded bead HEC (DC Bead®). As a follow-up to the preliminary study and the IDASPHERE I phase I study, we would like to evaluate the efficacy and confirm the safety of idarubicin-loaded beads for HEC using a protocol similar to PRECISION V, in a single-arm phase II setting.
Objectives	**Principal:** Objective response rate (complete and partial response) according to mRECIST **at 6 months** assessed in centralized review **Secondary:** Objective response rate (mRECIST) at 6 months assessed by the investigator Objective response rate at 6 months according to EASL criteria Time to treatment failure Best response according to mRECIST criteria Progression-free survival Overall survival Tolerance of the treatment Quality of life
Inclusion criteria	- Histologically proven HCC or according to EASL/Barcelona criteria for nodules ≥ 1 cm - Tumor not amenable to curative treatment (liver transplantation, surgical resection or percutaneous destruction) - Measurable targets according to mRECIST v1.1 criteria

	- Preserved liver function (in case of cirrhosis, Child-Pugh A or B7 without history of edemato-ascitic decompensation) - Tumor classified as BCLC A or B without portal or extrahepatic invasion or C if WHO = 1 - No prior treatment with chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy) - Age ≥ 18 years - WHO 0 or 1 - Biological workup: platelets ≥ 50,000/mm^3 , PNN ≥ 1,000/mm^3 , creatinine level ≤ 150 µmol/L - No heart failure (isotopic or echographic LVEF > 50%) - Signed informed consent
Non-inclusion **criteria**	- Advanced tumor disease (vascular or extrahepatic invasion including brain metastases or diffuse HCC with > 50% liver invasion) - History of other cancers excluding cancers known to be cured for more than 3 years (in this case histological evidence of HCC is required), or basal cell skin tumors or cervical cancer in situ adequately treated with curative intent - Previous treatment with idarubicin and/or doxorubicin - Contraindication to idarubicin (heart disease with myocardial insufficiency, severe renal or hepatic insufficiency, yellow fever vaccine) - Concomitant disease or severe uncontrolled clinical situation - Patients requiring long-term anticoagulant therapy - Thrombosis of the portal trunk or of a territory of 3 or more segments (or hepatofugal flow of the same territories) - Vascular involvement: o severe atheromatous disease or, o collateral vascular pathways potentially endangering normal territories during embolization or, o arteritis of the branches of the hepatic artery to be treated or, o arterio-port or arterio-sus-hepatic fistula not embolisable by coils - Pregnancy or breastfeeding - Lack of effective contraception (for men or women of childbearing age) - Patient who for psychological, social, family or geographical reasons could not be followed regularly - Concurrent participation of the patient in another experiment
Study design and treatment **plan**	1 to 4 chemoembolisations (CHE) with idarubicin-loaded microbeads (100-300 µm) (10 mg - Zavedos® Pfizer)
Statistical methods	The assumptions are: • H0: a proportion of patients with an objective response at 6 months of 25% or less is not acceptable • H1: A proportion of patients with an objective response at 6 months of more than 25% would show the effectiveness of the treatment. A rate of 40% is hoped for. Using a 2-stage Fleming design (Fleming, 1982) with a one-sided alpha risk of 5% and power of 90%, it is necessary to include **86 treated and evaluable patients**. At the 1ère stage: 43 patients will be included - If 10 or fewer patients have an objective response, the trial will be stopped for futility (H1 rejection) - If 18 or more patients have an objective response, the trial will be stopped for efficacy (rejection of H0) If not, we will go to 2ème step and include 43 additional patients. If 29 or more patients have an objective response, the treatment will be declared effective (rejection of H0) Taking into account a rate of 5% of lost to follow-up or not assessable, **91 patients** will be included. The decision rules will be adapted based on the number of evaluable patients actually included.
Biological studies	Analysis of VEGF level by ELISA technique and progastrin level then correlation with tumor and non-tumor liver volumes.
Number of subjects needed	91
Planned study period	Rate of 10 patients per month (1 patient per month per center - 10 centers) Expected start date of inclusions: September 2014. Expected completion date of inclusions (stage 2): July 2016 Expected completion of study: January 2020

EXAMINATION AND FOLLOW-UP SCHEDULE

	BEFORE TREATMENT	DURING TREATMENT with CHE			AFTER 6 MONTHS (patient follow-up)	
	Within 28 days before 1ière HEC and before inclusion	Before each HEC	After each HEC	At 6 months after inclusion	1ière year every 3 months	2ième year every 6 months
Clinical and biological informed consent	X					
CLINICAL EXAMINATION						
Weight, height, pain assessment (VAS)	X	X			X	
General status WHO	X	X			X	
Child-Pugh if associated cirrhosis and BCLC score	X					
Quality of life (QLQ-C30 and HCC-18)	X	X				
Description of the disease and medical history	X	X				
Toxicity assessment (NCI-CTC v4.0)			X	X		
MORPHOLOGICAL EXAMINATIONS* (IN FRENCH ONLY)**						
Hepatic MRI	X		X	**X**	X****	X****
Ultrasound of the liver					X****	X****
CAT scan for extra-hepatic evaluation	X		X (in case of contraindication to MRI)	**X**	X (thoracic every 6 months)	X (thoracic)
Portal Doppler if thrombosis is suspected on imaging	X	X (recommended)				
ECG	X					
Evaluation of left FEV	X					
BIOLOGICAL ASSESSMENT						
Biological check-up	X*	X**			X (liver test)	X (liver test)
AFP marker	X				X	X
Serology (HBsAg, anti-HBs, anti-HCV)	X					
Pregnancy test (within 7 days of inclusion)	X					
BIOLOGICAL STUDY						
Samples: 2 EDTA tubes of blood then centrifugation for aliquoting of 4 cryotubes of plasma and freezing at -20°C then -80°C		X (D0, D1, D2 and D3 of 1ière HEC)				
IMAGERY* : CT cone beam or CT scan without injection during the procedure						

* Complete biological check-up: CBC/platelets, PT, AST, ALT, alkaline phosphatases, GGT, bilirubin (total, free and conjugated), factor V, blood ionogram, creatinine, albumin, blood sugar, blood calcium

** Biological check-up before each HEC: CBC, platelets, blood ionogram, creatinine, albumin, ASAT, ALAT, PAL, GGT, total and conjugated bilirubin, PT

***** :** An anonymized copy of the imaging is to be sent to the FFCD for centralized review

**** : hepatic MRI (or CT) / ultrasound of the liver by a trained operator alternating every 3 months for 2 years

I. OBJECTIVES OF THE TRIAL

I.1 Main objective

The objective of this non-randomized phase II study is to evaluate the objective response rate (complete and partial response) at 6 months, assessed according to the mRECIST criteria in centralized review.

I.2 Secondary objectives

The secondary objectives of this study are to evaluate:

- The investigator-assessed 6-month objective response rate (mRECIST)
- Time to treatment failure
- The best answer according to mRECIST
- Objective response rate at 6 months (EASL)
- Progression-free survival
- Overall survival
- Tolerance of the treatment
- Quality of life (QLQ-C30 questionnaires and its HCC18 module specific to HCC)

II. PATIENT SELECTION

II.1 Inclusion criteria

- Histologically proven HCC or according to EASL/Barcelona criteria for nodules $\geq$ 1 cm
- Tumor not amenable to curative treatment (liver transplantation, surgical resection or percutaneous destruction)
- Measurable targets according to mRECIST v1.1 criteria
- Preserved liver function (in case of cirrhosis, Child-Pugh A or B7 without history of edemato-ascitic decompensation)
- Tumor classified as BCLC A or B without portal or extrahepatic invasion or C if WHO= 1
- No prior treatment with chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy)
- Age $\geq$ 18 years
- WHO 0 or 1
- Biological workup: platelets $\geq$ 50,000/mm^3 , PNN $\geq$ 1,000/mm^3 , creatinine level $\leq$ 150 µmol/L
- No heart failure (isotopic or echographic LVEF > 50%)
- Signed informed consent

II.2 Non-inclusion criteria

- Advanced tumor disease (vascular or extrahepatic invasion including brain metastases or diffuse HCC with > 50% liver invasion)
- History of other cancers excluding cancers known to be cured for more than 3 years (in this case histological evidence of HCC is required), or basal cell skin tumors or cervical cancer in situ adequately treated with curative intent
- Previous treatment with idarubicin and/or doxorubicin
- Contraindication to idarubicin (heart disease with myocardial insufficiency, severe renal or hepatic insufficiency, yellow fever vaccine)
- Concomitant disease or severe uncontrolled clinical situation
- Patients requiring long-term anticoagulant therapy
- Thrombosis of the portal trunk or of a territory of 3 or more segments (or hepatofugal flow of the same territories)
- Vascular involvement:

    - severe atheromatous disease or,
    - collateral vascular pathways potentially endangering normal territories during embolization or,
    - arteritis of the hepatic artery branches to be treated, or
    - arterio-port or arterio-sus-hepatic fistula not embolisable by coils
- Pregnancy or breastfeeding
- Lack of effective contraception (for men or women of childbearing age)
- Patient who for psychological, social, family or geographical reasons could not be followed regularly
- Concurrent participation of the patient in another experiment

III. PRE-INCLUSION ASSESSMENT

To be performed within 28 days prior to treatment and before inclusion:

Full clinical examination:
- Weight, height, vital signs, WHO index, pain assessment (VAS)
- Child-Pugh score if associated cirrhosis, BCLC (Barcelona Clinic Liver Cancer) score (Appendix 4)
- Medical history
- Description of the disease
- Quality of life (QLQ-C30 and its module HCC18)

Complete biological workup:
- CBC, platelets, PT, AST, ALT, PAL, GGT, bilirubin (total, free and conjugated), factor V, blood ionogram, creatinine, albumin, blood glucose, blood calcium
- Markers: α-fetoprotein (AFP)
- Serology: HBsAg, anti-HBc, anti-HCV,
- Pregnancy test for women of childbearing potential (β-HCG) within 7 days prior to inclusion, then effective contraception throughout the study

Morphological assessment:
- Liver MRI documenting at least one measurable liver lesion according to mRECIST 1.1 criteria
- Thoracoabdomino-pelvic CT for extrahepatic evaluation. In case of contraindication to MRI, CT can be used to evaluate the response
- Portal Doppler if portal thrombosis is suspected on imaging
- ECG within 7 days prior to chemoembolization
- Left ventricular ejection fraction (isotopic or ultrasound) (LVEF) within 4 weeks prior to 1^{ière} HEC

IV. INCLUSION

After the patient has signed the clinical consent form (Appendix 1) and verified the results of the examinations required for inclusion in the study, the patient can be registered.

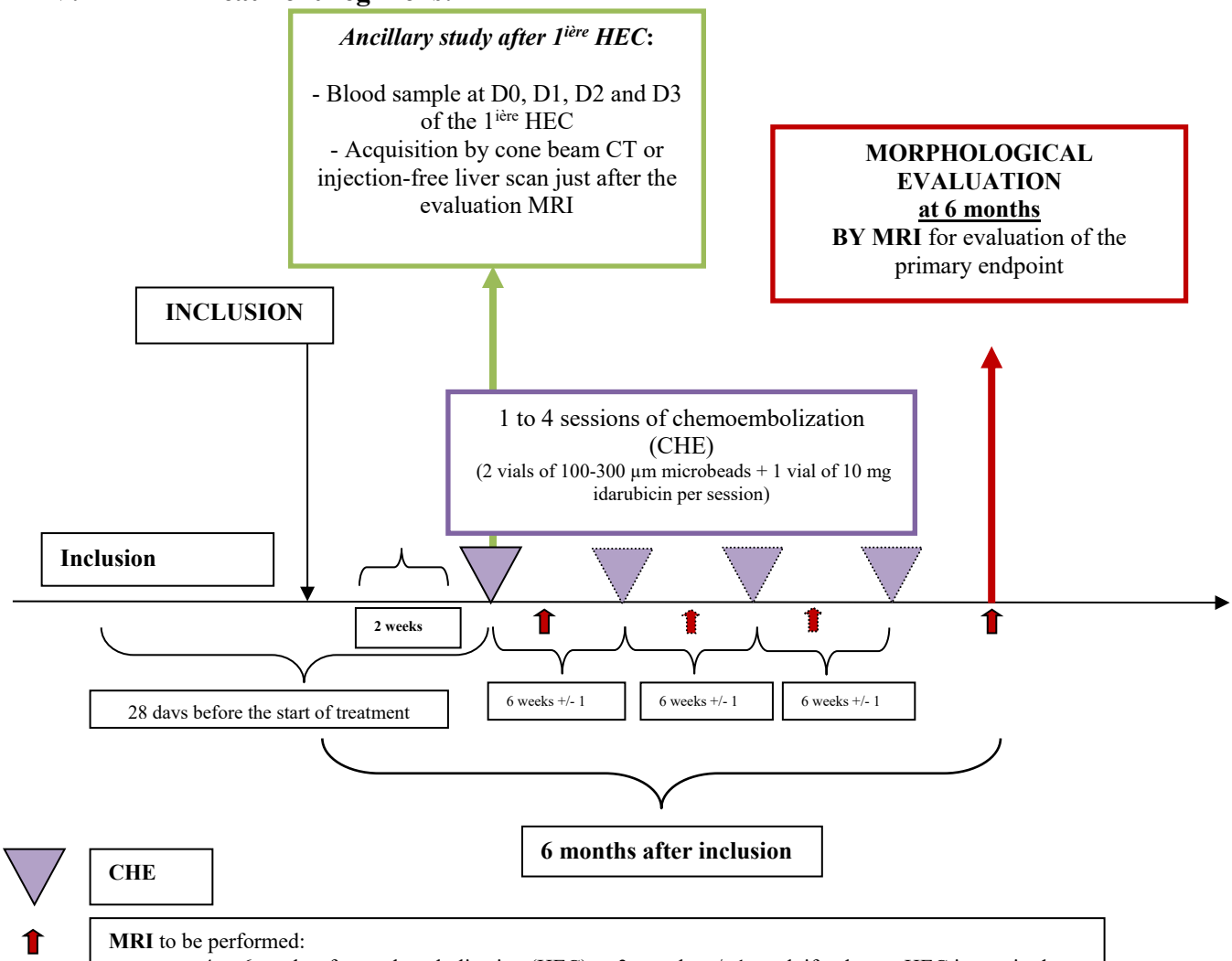
The registration number will be assigned by faxing the inclusion form to **03 80 38 18 41**. The FFCD's Randomization - Management - Analysis Center in Dijon is open Monday to Friday from 9:00 am to 6:00 pm.

An observation booklet will be sent out at the opening of the center, then an observation booklet will be sent out after each inclusion.

After inclusion in the study, treatment should begin within a maximum of 2 weeks.

V. TREATMENT

V.1 Treatment regimens:



V.2 Description of the experimental treatment and medical device

Investigational treatment and investigational medical device:

Microbeads (medical device, 2 vials DC Bead® 100-300µm per HEC, Biocompatibles, UK) and idarubicin (experimental treatment, 10 mg vial of powder for solution, Zavedos®, Pfizer, France) are provided by the Sponsor for this research.

The vials of microbeads and idarubicin will be labeled according to current good practices. The idarubicin will be dispensed by the company LC2.

Non-experimental treatments:

Contrast media for HEC: When performing chemoembolization, the interventional radiologist should add a **non-ionic** contrast medium to the loaded microspheres before injecting them (see paragraph V.2.3). This is to

avoid discharging the microspheres (+ - bond between the bead and idarubicin). The authorized contrast products for chemoembolization are Visipaque® (iodixanol), Ivepaque® (iopentol), Omnipaque® (iohexol), Xenetix® (iobitridol), Iopamiron® (iopamidol), Ultravist® (iopromide), Iomeron® (iomeprol).

Contrast media for evaluation of responses to HEC: The contrast media used to perform MRI (or CT in case of contraindication to MRI) morphological evaluations are left to the choice of the investigator according to the habits of the centers (non-experimental drug, in its indication).

V.2.1 Storage conditions, labeling and traceability of investigational drugs

Storage:
Vials of idarubicin 10 mg powder for solution (Zavedos®) and vials of microbeads (DC Bead 100-300 µm) should be stored at a temperature not exceeding 25°C.
The stability of idarubicin-loaded microbeads is 4 days in the dark and at a temperature between +2°C and +25°C.

Labeling of experimental products:
The experimental products (idarubicin and microbeads) will be labeled according to the regulations in force.
The labels will include the legal information including the lot number, the expiration date, the mention "FFCD 1307 clinical trial", the contact information of the Sponsor and the coordinator.
Each vial of microbeads and idarubicin will have a unique number on the label. These labels will be stuck on the traceability sheet.

Traceability of experimental products:
A traceability sheet is set up within the framework of the study for each chemoembolization and per patient.
The pharmacist should prepare the microbeads the evening before the chemoembolization session:

- detach the labels of the 2 vials of microbeads (100-300µm) **and** the vial of idarubicin 10 mg
- stick these labels on the traceability form provided for this purpose, filling in the initials of the patients and the study inclusion number (these forms are included in the pharmacy kit sent at the opening of the center)
- make available to the FFCD CRA during its monitoring, the completed forms of all patients included in the study in the center. A copy will be kept in the pharmacy and the original will be sent to the FFCD
- empty vials can be destroyed before monitoring provided that the labels have been removed and glued on the patient's traceability sheet

If after preparation of the syringe containing the idarubicin-beads mixture, the administration is not finally done, mention on the traceability sheet, next to the glued labels, that the administration has not been done. The preparation can be destroyed when it expires (after 4 days).

V.2.2 Preparation of microbeads for HEC

The idarubicin solution loaded with 100-300 µm embolization microbeads (DC Bead) should be prepared under a vertical laminar airflow hood or isolator to protect the handler and to ensure aseptic preparation.

=> Reconstitute with 5 mL of water for injection, 1 vial of 10 mg of idarubicin powder (Zavedos®).
=> Take in a 30 ml syringe, the totality of two vials of DC Bead 100-300 µm (microbeads + supernatant).
=> The supernatant in the syringe should be removed vertically into a bag (empty or saline bag that should be put aside). However, always make sure that the beads in the syringe are never completely dry in order to prevent them from clumping together.
=> Then insert the syringe of idarubicin (10 mg in 5 ml) into the 30 ml syringe containing the beads.
=> Let the mixture rest for 4 hours by regularly turning over the contents of the syringe. The color of the mixture becomes dark orange which indicates the loading. This one is complete (> 95%, measured by mass spectrometry) after 4 hours.
=> At the end of the loading, position the syringe vertically to remove a good part of the supernatant in a 50 ml bag of saline, for example, which will be immediately discarded.
=> Adjust the final volume to 8 ml (2x2 ml of beads) and adapt a 3-way valve or equivalent device

=> Immediately after, the syringe will be wrapped in aluminum foil or an opaque sheath or any other material that protects the syringe from light and then packaged in a protective sheath double sealed at both ends according to the pharmacy's habits
=> The preparation will be transported to the radiology department in a sealed rigid box according to the center's habits.

A slide show illustrating this preparation will be given to the pharmacists during the implementation in the centers.

V.2.3 Methods of administration

The DC Beads are diluted in a **non-ionic** contrast solution (5-10ml of contrast for 1ml of beads) to allow a fluid diffusion within the catheter. The DC Beads must be injected slowly, at a flow rate of approximately 1 ml/min, in order to limit the risk of reflux or obstruction of the catheter. The use of a microcatheter is recommended in order to obtain an ultra-selective positioning, especially in case of localized disease.

The injection should be performed until sub-stasis is observed in the artery supplying the tumor (i.e., the contrast should wash out in 2 to 5 systoles). At this point, the injection must be stopped regardless of the dose of charged beads injected to avoid reflux. As soon as this phenomenon is reached no additional embolization material should be injected.

If there is still a sub-stage-free flow after injection of all loaded beads, no additional material should be injected (Lencioni *et al.* , CVIR 2012).

SUPRA-SELECTIVE APPROACH:
For patients with 1 to 3 nodules, a supra-selective (segmental, sub-segmental) approach should be used with equitable distribution of the idarubicin dose within the lesions. The use of a microcatheter is recommended. If a supra-selective approach is impossible, a lobar approach should be used (see below).

LOBAR APPROACH:
For patients with bilobar involvement (or unilobar >3 nodules, or <3 nodules without the possibility of a supra-selective approach technique), each lobe should be treated separately at each session. A microcatheter should be placed in a lobar artery and the total dose of idarubicin administered. Loaded beads should not be injected into the cystic artery or the right gastric artery. If there is a risk of injection into these arteries, they should be previously embolized with coils, or the microcatheter should be positioned downstream to avoid injection into these arteries. To avoid the cystic artery, it is recommended to catheterize the sectorial branches (downstream of the origin of the cystic artery) separately and to inject the loaded beads equally into each branch.

For evaluation of response to treatment (primary endpoint), perform MRI 4-6 months after each HEC.
Except in the case of bilobar disease (for which 2 sessions of HEC should be scheduled upfront), retreatment (new HEC treatment) will be performed according to follow-up MRIs. An MRI will be performed 4 to 6 weeks after each chemoembolization treatment. In case of tumor remnant or recurrence treatable by HEC (i.e., no portal trunk thrombosis or in a territory $\geq$ 3 segments, hepatopoietic portal flow, WHO status < 2, no hepatic decompensation, no extrahepatic metastasis), a new course of HEC should be performed targeting the remnant or recurrence (same distinction as above: supra-selective OR lobar approach). In the absence of tumor remnant or recurrence on MRI performed 4-6 weeks, MRI surveillance is performed every 3 months and the modalities of retreatment are the same as before.

In all cases, MRI at 6 months from the date of inclusion must be performed (primary endpoint of the study).

At the end of the session, embolization with additional material is not recommended.

If in case of a single HEC, a recurrence of the disease is observed at the 3-month MRI, a second HEC can be performed and will be performed as part of the protocol.

V.3 Premedication and concomitant treatments

Sufficient hydration (up to 2 liters per day), adapted to the cirrhotic context, will be prescribed before and after chemoembolization for at least 48 hours.

In case of nausea or vomiting, provide adequate treatment according to center procedures.

After the procedure, level 1 to 3 (WHO) analgesics will be used in an appropriate dose.

At the end of the procedure, the pain felt by the patient will be recorded using a visual analog scale (VAS rated from 0 to 10). If VAS > 3, titration of IV morphine by an IDE according to the recommendations.

Any treatment required for patient comfort will be prescribed at the discretion of the investigator.
The use of a preventive anti-emetic treatment is recommended.

VI. EXPECTED TOXICITIES AND DOSE ADJUSTMENT

VI.1 Chemoembolization

The main adverse effects expected with chemoembolization are:

- Unwanted reflux or passage of microbeads into normal arteries adjacent to the targeted lesion or through the lesion to other arteries or arterial beds
- Non-targeted embolization
- Pulmonary embolization
- Ischemia in an undesired location
- Capillary bed saturation and tissue damage
- Rupture of a vessel or lesion and hemorrhage
- Neurological deficits including cranial nerve palsy
- Vasospasm
- Deaths
- Re-permeabilization
- Foreign body reactions requiring medical intervention
- Infection requiring medical intervention
- Catheter tip clot formation and subsequent mobilization

Expected effects related to the embolization procedure (from CNIHM anticancer files November 2008)

- Fever, hypochondrial pain, vomiting
- Transient thrombocytopenia and liver dysfunction
- Increased transaminases (cytolysis)
- Local ischemic and septic manifestations (cholecystitis, hepatic infarction, hepatic abscess, digestive hemorrhage)
- Renal insufficiency
- Hematoma at the puncture site
- Acute lower limb ischemia

Adaptation for chemoembolization

The interval between chemoembolization sessions should be 6 weeks plus or minus 1 week. Any additional time must be agreed upon by the coordinator.

HEC Session Rehearsal:

The chemoembolization session(s) are scheduled every 6 weeks, plus or minus 1 week.

The imaging technique, after each session, will be MRI and a cone beam CT acquisition (after 1^{ière} HEC for the translational study and after, if possible, each HEC to assess the quality of chemoembolization.

Subsequent sessions will be performed according to tumor response. No additional session is recommended in case of complete tumor response according to the modified RECIST criteria (mRECIST) (Appendix 2) or progression of a previously chemoembolized tumor.

In case of non-hematological toxicity of grade 3 or 4 attributable to HEC, no additional HEC is performed. In case of bleeding and/or severe liver failure and/or other toxicities secondary to a grade ≤ 3 chemoembolization session, the next session(s) will be performed at the discretion of the investigator.

Transient increases in ALT and/or AST in the 24-48 hours after HEC do not lead to failure to perform additional HEC. Indeed, this transient increase does not have a significant impact (R Sacco et al, Clinical impact of selective transaerterial chemoembolization on heptaocellular carcinoma: A cohort study. World J Gastroenterol 2009 April 21; 15(15): 1843-1848).

VI.2 Idarubicin

The main effects expected for idarubicin (Zavedos® powder for solution for infusion) according to the current versions of the SPCs (version of 6/07/2006 appendix 8) are the following

- Significant spinal cord hypoplasia which can be responsible for serious or even fatal conditions
- Alopecia reversible on discontinuation of treatment
- Digestive disorders: nausea, vomiting, diarrhea
- Stomatitis, esophagitis
- Elevated liver enzymes and bilirubin in 20-30% of cases
- Skin rash
- Acute heart rhythm disturbances, acute or late heart failure (rare before a cumulative dose of 93 mg/m²)
- Red coloration of the urine 24 to 48 hours after treatment.

As with other DNA altering anticancer agents, myelodysplastic syndromes and acute myeloid leukemias have been observed after combination therapy with anthracycline.

In case of idarubicin-related effects, no dose adjustment of idarubicin for loading the microbeads is planned. The chemoembolization session is then postponed or cancelled.

VII. MONITORING DURING AND AFTER TREATMENT

VII.1 Before each HEC

- Complete clinical examination: weight, vital signs, WHO general condition (which should be 0 or 1), pain assessment (VAS)
- Biological work-up: CBC/platelets, blood ionogram, creatinine, albumin, transaminases (AST, ALT), alkaline phosphatases (ALP), GGT, total and conjugated bilirubin, PT
- Adverse event evaluations of previous HECs according to NCI CTC version 4.0
- Quality of life questionnaires (QLQ-C30 and its module HCC18)

Prior to the session, the investigator should ensure that the patient has adequate hepatic and hematological function:

- Bilirubin $\leq$ 1.5mg/dL, PNN $\geq$ 1,000/mm3, platelets $\geq$ 50,000/mm3, creatinine level $\leq$ 150 µmol/L
- Hepatopoetic flow, thrombosis is considered significant if it involves at least 3 segments. The procedure is then contraindicated. A Doppler is strongly recommended before the embolization sessions to ensure that the procedure can be performed. It is recommended to evaluate these criteria according to the habits of the center.

For patients participating in the translational study: blood sampling for translational study (see paragraph IX)

VII.2 After each HEC

Hepatic MRI (or CT scan in case of contraindication to MRI) will be performed 4 to 6 weeks after each chemoembolization to assess their effectiveness.

Assessment imaging at 6 months from the date of inclusion MUST be performed regardless of the time of last HEC to assess the primary endpoint of the study.

Target measurements will be done according to mRECIST v1.1 to assess the primary endpoint of the study and according to EASL criteria to assess the secondary endpoint (Appendices 4 and 5).

An **anonymized copy on CD ROM** (present in each observation book) **of each morphological evaluation** until progression (even if beyond 6 months) (MRI) is to be made. **The copies will be sent to the CRGA of the FFCD for centralized review .**

For the translational study, perform a cone beam CT acquisition or a hepatic CT scan without injection at the time of the 1ière HEC.
For the clinical study, if possible, perform a cone beam CT acquisition at each HEC to assess the quality of the chemoembolization.

VII.3 Post-treatment monitoring beyond 6 months after inclusion:

After the end of chemoembolization treatment, patients will be followed according to TNCD recommendations:

Clinical and biological evaluation every 3 months for the first year and then every 6 months for 1 year:

- Clinical examination (weight, WHO)
- Biological tests: liver tests (ASAT, ALAT, GGT, bilirubinemia, albuminemia, TP)
- Marker : AFP

Morphological assessment:

- Chest CT scan without injection, every 6 months for 2 years
- Hepatic MRI (or CT scan) - liver ultrasound by a trained operator alternating every 3 months for 2 years

Monitoring data will be collected in the observation book during this 2-year period.

VIII. STOP PROCESSING THE STUDY

The processing of the study will be stopped in case of:

- Investigator's decision
- Major toxicity requiring discontinuation of treatment
- Serious or unexpected event requiring discontinuation of protocol treatment
- Progression of the disease
- Patient refusal or withdrawal of consent
- Death of the patient

In all cases of treatment discontinuation, the patient remains in the analysis for intention-to-treat and overall survival, and for 30 days after the last study treatment for toxicity.
There is no exclusion period for a subsequent therapeutic trial.

IX. TRANSLATIONAL STUDY

Only patients who have signed their translational-biological informed consent will be collected.
Rationale for the study (see Appendix 15).

Blood sampling for VEGF determination
- 4 sampling times:
After the 1ière HEC at D0, D1, D2 and D3

- Samples :
At each sampling time (4 times), collect 2 x 7 ml EDTA tubes of blood.
Centrifuge the blood tubes at room temperature at 1000 g for 15 minutes.
Collect the plasma to be distributed in a minimum of 4 cryotubes (minimum 1 mL per cryotube).
Identify the cryotubes with the patient's initials + inclusion number in the study, the sampling times.
Freeze the 2 plasma cryotubes at -20°C then at -80°C.
Note: The time between collection and freezing (at -20°C) of plasma should not exceed 1 hour.

Complete the sample census form (present in the study investigator's binder) and send it by fax (03 80 38 18 41) or by email (marie.moreau@u-bourgogne.fr) to the FFCD as soon as the 4 sampling times have been completed.

The repatriation of the samples to the CRB (biological resource center) EPIGENETEC of the FFCD, will be done at the end of the study by a specialized carrier.

Imaging for correlation with VEGF assay
Perform a cone beam CT or CT scan without injection after the 1ière HEC.
An anonymized copy should be sent to the FFCD. A blank CD ROM is provided in the patient's CRF.

X. CENTRALIZED READING OF MRI AND CT

Responses will be evaluated according to the mRECIST version 1.1 (primary endpoint) and EASL (secondary endpoint) criteria (Appendices 4 and 5) and will be reviewed by a panel of independent radiologists who will confirm responses and dates of tumor progression or recurrence once all study examinations have been retrieved.
For this purpose, an **anonymized copy on CD ROM** (present in each observation book) **of each morphological evaluation until progression** (even if beyond 6 months) (MRI) is to be made. **The copies will be sent to the CRGA of the FFCD for centralized review.**

XI. MANAGEMENT OF SERIOUS ADVERSE EVENTS (SIA)

1. Security assessment parameters

Safety will be assessed by evaluating the general and clinical condition of patients and by collecting events occurring between visits during consultations. Toxicities will be assessed using the NCI-CTC-AE version 4.0 toxicity scale (see Appendix 6).

In case of an emergency, the patient, his family or his physician should call the investigator to warn of an event.

2. Definitions

a. Adverse Event (AE)

An adverse event is a harmful occurrence in a person who is a subject of biomedical research, whether or not the occurrence is related to the research or the product being investigated.

All adverse events will be recorded in the observation book on the pages provided.

b. Serious Adverse Event (SAE)

A serious adverse event (SAE) is considered to be any event:

- Resulting in death,
- Life-threatening,
- Leading to hospitalization or prolonged hospitalization,
- Causing permanent disability or severe temporary incapacity,
- Causing a birth defect, fetal malformation or abortion,
- Medically significant.

The terms disability and incapacity correspond to any temporary or permanent physical or psychological handicap, clinically significant and affecting the physical activity and/or quality of life of the patient.

Any clinical event or laboratory result considered serious by the investigator and not corresponding to the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome corresponding to one of the above mentioned severity criteria (e.g. overdose, second cancers, pregnancies and new events may be considered as medically significant).

c. Undesirable Effect

Any noxious and undesired reaction to an investigational drug at any dose or to any investigational component. The adverse reaction is serious if it meets the severity criteria (see above)

d. New Fact

A new fact can be: an unexpected frequency of an expected SAE, an SAE related to the trial procedure, insufficient efficacy in life-threatening diseases,...

e. Intensity (or severity)

The intensity criterion should not be confused with the severity criterion, which is used as a guide to define reporting obligations.

The intensity of the events will be estimated according to the extract of the CTC-AE version 4.0 classification (see Appendix 6). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Mild (grade 1): does not affect the patient's usual daily activity
Moderate (grade 2): disrupts the patient's usual daily activity
Severe (grade 3): prevents the patient's usual daily activity
Very Severe (grade 4): requires resuscitative measures/ life threatening
Death (grade 5)

f. Unexpected Serious Adverse Effect

An unexpected serious adverse reaction is an event that is not mentioned, or that differs in nature, intensity, or evolution from the product's reference document.

In this test, the reference documents for the products used are:

- For microbeads: the DC Beads user manual (current version)
- For idarubicin: ZAVEDOS® Summary of Product Characteristics (current version)

3. <u>What to do in case of a serious adverse event</u>

a. Investigator's responsibility

The investigator informs the sponsor of all Serious Adverse Events (Expected and Unexpected), whether or not attributable to the research, that occur during the study or within 30 days (to be adapted according to the protocol) after the last administration of treatment.

All Delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to the protocol treatment(s) or research should be reported without time limitation.

The declaration is made by sending by fax the "notification of a serious adverse event" form (cf. appendix 10) documented as precisely as possible, dated and signed, within 24 working hours following their observation to: 03 80 38 18 41

The investigator will note for each event, among other things:

- Its description as clearly as possible according to medical terminology,
- Intensity,
- The start and end date of the event,
- The measures undertaken and whether or not corrective treatment is necessary,
- If the trial treatment was discontinued,
- Its evolution. In the case of a non-fatal event, the evolution will have to be followed until the recovery or the return to the previous state or the stabilization of possible after-effects,
- The causal relationship between this event and the treatment being tested or a constraint related to the research (period without treatment, additional examinations requested as part of the research, etc.),
- The causal relationship with the condition treated, another condition or another treatment. The investigator must also attach to the serious adverse event report, whenever possible:
    - A copy of the hospitalization or extension of hospitalization report,
    - A copy of the autopsy report if required,
    - A copy of all results of additional tests performed, including relevant negative results, with the normal laboratory values attached,
    - Any other document that it deems useful and relevant.

All these documents must be anonymized.
Additional information may be requested (by fax, telephone or during a visit) by the monitor and/or the promoter.

b. Responsibility of the promoter

Upon receipt of the investigator's report of the serious adverse event, the sponsor should issue an opinion on the causal relationship between the serious adverse event and the study product(s).
If the serious adverse event is related by the investigator and/or sponsor to one of the study products (i.e., it is a serious adverse event), the investigator and/or sponsor must establish the expected or unexpected nature of the event.
If it is a serious unexpected adverse reaction, or if it is a new fact, the sponsor writes an initial report which will be transmitted to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in case of death, otherwise within 15 days.
If it is an expected serious adverse event, it will be collected for the semi-annual and annual safety reports.

4. Modalities and duration of follow-up of individuals following the occurrence of adverse events.

The investigator is responsible for appropriate medical follow-up of patients until resolution or stabilization of the effect or until the patient's death. This may sometimes mean that this follow-up extends beyond the patient's discharge from the trial.

He/she transmits the additional information to the sponsor using an SAE reporting form (checking the Follow-up No. X box to specify that it is a follow-up report and not an initial report) within 24 hours of obtaining it. It also forwards the last follow-up to the resolution or stabilization of the SAE.

He keeps the documents concerning the suspected adverse reaction in order to allow, if necessary, to complete the information previously transmitted.

It responds to requests for additional information to document the initial observation.

XII. STATISTICAL ANALYSIS

XII.1 Provisional timetable for the study

With an expected rate of one patient per month per center, i.e. 10 patients per month, and with a suspension of inclusions between stage 1 and 2, the study schedule will be as follows:

Stage 1: 43 evaluable patients
- Expected start date of inclusion (stage 1): September 2014
- Anticipated end date of inclusion stage 1: February 2015
- Judging criterion at 6 months: August 2015
- Stage 1 analysis (+ 6 months): February 2016

Stage 2: 43 evaluable patients
- Expected start date of inclusion: February 2016
- Expected completion date of inclusion stage 2: July 2016
- Judging criterion at 6 months: January 2017
- Final analysis of primary endpoint (+ 6 months): July 2017
- 2-year overall survival analysis: January 2020

XII.2 Judging criteria

XII.2.1 Main criterion

The primary endpoint is the rate of patients with objective response (complete response or partial response) **at 6 months after inclusion** according to mRECIST criteria and centralized review.

XII.2.2 Secondary Criteria

The secondary endpoints of this study are:

- The rate of patients in objective response (complete response or partial response) at 6 months according to mRECIST criteria and evaluated by the investigator.

- The rate of patients in objective response (complete response or partial response) at 6 months according to EASL criteria assessed by the investigator and in centralized review.

- Time to treatment **failure**
It is defined as the time interval between the date of inclusion and the date of protocol treatment failure. Death, progression, and any discontinuation of protocol treatment (regardless of cause) are considered treatment failures.
Patients alive without failure will be censored at the date of the last 6-month morphological evaluation.

- **The best response** according to the mRECIST criteria

- Progression-free survival
It is defined as the time interval between the date of inclusion and the date of 1st progression according to mRECIST criteria (assessed in centralized review) or death (regardless of cause).
Patients living without progression will be censored at the date of last news.

- Overall survival
It is defined as the time interval between the date of inclusion and the date of death (regardless of cause) or the date of last news for living patients.

- Tolerance of the treatment
Toxicities will be evaluated by the NCI-CTC v4.0 criteria. They will be described according to their grade in terms of number of toxicities and number of patients who experienced the toxicity.

- Quality of life (QLQ-C30 questionnaires and its HCC18 module specific to HCC)

XII.3 Calculation of the number of subjects needed

The assumptions are:

- H0: A proportion of patients with an objective response at 6 months of 25% or less is not acceptable
- H1: A proportion of patients with an objective response at 6 months of more than 25% would demonstrate the effectiveness of the treatment. A rate of 40% is hoped for.

Using a 2-stage Fleming design (Fleming, 1982) with a one-sided alpha risk of 5% and power of 90%, it is necessary to include **86 treated and evaluable patients**.

At the 1ère stage: 43 patients will be included

- If 10 or fewer patients have an objective response, the trial will be stopped for futility (H1 rejection)
- If 18 or more patients have an objective response, the trial will be stopped for efficacy (rejection of H0)

If not, we will go to 2ème step including 43 additional patients

If 29 or more patients have an objective response, the treatment is declared effective (rejection of H0)

Taking into account a 5% rate of patients lost to follow-up or not evaluable, **91 patients** will be included.
The decision rules will be adapted based on the number of evaluable patients actually included.

XII.4 Statistical analysis plan

A statistical analysis plan will be written prior to freezing the database.

Analysis Populations:

The characteristics of the patients included in the study will be described in strict intention-to-treat (ITT).
Efficacy analyses will be performed on a modified intention-to-treat (mITT) basis: all evaluable patients included in the study regardless of eligibility criteria. A patient is considered evaluable if he/she has had at least one chemoembolization and one post-treatment evaluation.

Population evaluable for safety:
The ITT population that received at least one chemoembolization.

***Statistical analysis*:**

The description of the variables will be done using percentages (95% confidence interval) for qualitative variables and using mean (standard deviation) and median (Min-Max) as well as the inter-quartile range (Q1-Q3) for quantitative variables.

The estimation of censored data will be done by the Kaplan Meier (KM) method. Times will be described by medians and rates at different time points with their 95% confidence intervals. The median follow-up time will be calculated using the reverse Kaplan Meir method.

XII.5 Independent Committee

An independent committee composed of 1 clinician / 1 methodologist-statistician / 1 pharmacovigilant expert / 1 radiologist will be set up before the beginning of the trial. It will meet regularly during the course of the study according to the rate of inclusion.
It will have to rule on the declared ADRs. It can also be seized at any time by the Sponsor in case of significant facts on the tolerance (ADRs and AEs) of the treatment.

XIII. JUSTIFICATION OF THE TEST

A systematic review published by Marelli et al. showed that the most commonly used products in HEC were doxoxrubicin (36%), cisplatin (31%) and epirubicin (12%) [Marelli et al., CVIR 2007]. However, until recently, there was no clear rationale for choosing one molecule over another. Indeed, systemic chemotherapy is considered ineffective in HCC [Burrough, Lancet Oncol 2004], which does not provide an argument for the choice of the molecule. Moreover, 2 randomized trials that were designed to compare agents (doxorubicin versus epirubicin) were negative in terms of survival [Kawai, Sem Oncol 1997; Watanabe, Cancer Chemoth Pharm 1994].
Very recently, a study conducted at the University Hospital of Dijon, compared the cytotoxicity of various anticancer agents on HCC cell lines, with the aim of selecting the best candidate for HEC (Boulin et al., Anticancer drugs 2011).
Eleven chemotherapy agents were tested, including those most commonly used for HEC. Idarubicin (an anthracycline) was by far the most effective in vitro. The superiority of idarubicin (over doxorubicin) was observed particularly in the SNU-449 line, which is known to be resistant to several chemotherapy agents [Park, JNCI 1994]. The better cytotoxicity of idarubicin can be explained by 2 mechanisms: 1) idarubicin has a better intracellular penetration than other anthracyclines [Broggini, Cancer Treat Rep 1984]. This is probably due to its greater lipophilicity, thus facilitating its passage through the membrane composed of a double lipid layer, 2) idarubicin has the property of resisting the multidrug resistance (MDR) system [Roovers, Leuk Res 1999]. The MDR mechanism, often observed in HCC, consists of membrane pumps that transport the molecule out of the cell. These two properties could explain a higher accumulation of idarubicin in HCC cells and thus a better efficacy. Interestingly, idarubicin administered orally (5mg/day for 21 days) has been shown to have low toxicity and efficacy in HCC [Tumolo, ASCO 2002]. Currently, idarubicin is used to treat leukemia. Its safety profile (in particular hematological and cardiac) is known.

Based on these findings, a pilot study was conducted to evaluate the safety and efficacy of lipiodol-based HEC using a dose of 10 mg idarubicin in 21 patients with unresectable HCC. These preliminary data show that HEC with idarubicin is effective and has low toxicity (Favelier et al., CVIR 2013).

As idarubicin can be loaded on microbeads, a phase I study (IDASHPERE) (article submitted to Clin Cancer Research) with DC Bead® (300-500µm) loaded with idarubicin (dose escalation from 5 to 25 mg) was conducted at the Dijon University Hospital. DLT and MTD were determined in 21 patients using a CRM (Continual Reassessment Method). The MTD of idarubicin was evaluated at 10 mg. In this study, idarubicin-loaded beads did not pose any specific toxicity concerns.

The 10-mg dose is consistent with the well-known toxicity profile of idarubicin: cumulative cardiotoxicity of doxorubicin is observed from 550 mg/m², whereas that of idarubicin is observed from 93 mg/m². Thus, there is a 5.9:1 ratio between their cumulative toxicities. The most commonly used (and also the lowest) dose for doxorubicin-based HEC is 50 mg. The dose equivalent of idarubicin would therefore be: 50 mg (doxorubicin) / 5.9 (doxorubicin/idarubicin ratio) = approximately 10 mg of idarubicin.
It has already been shown that the hepatic extraction of idarubicin is better than that of doxorubicin and daunorubicin in an animal model of sarcoma. In this study, the AUC 0-48h and AUC 0-72h) were 1.35 times higher with idarubicin, showing that the intrahepatic penetration of the molecule was 35% higher [Broggini M et al. Cancer Treat Rep 1984].

The PRECISION V randomized phase II trial compared conventional HEC (cCHE) with doxorubicin-loaded bead HEC (DC Bead®) in patients with HCC (Lammer et al. CardioVasc Intervent Radiol. 2010). This is the largest published study of HEC. The PRECISION V data can therefore be used for comparison with other studies in terms of efficacy and safety.

As a follow-up to the preliminary study and the IDASPHERE Phase I study, we would like to evaluate the efficacy and confirm the safety of idarubicin-loaded beads for HEC in a protocol similar to PRECISION V, in a single-arm Phase II setting.

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XV. LEGAL AND ETHICAL ASPECTS ADMINISTRATIVE CONSIDERATIONS

XV.1 STUDY SPONSOR

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the number EudraCT 2014-000050-10.

XV.2 REMINDER OF THE TEXTS IN FORCE

This test will be carried out according to the European Directive 2001/20/EC.

XV.3 PUBLIC LIABILITY INSURANCE

Insurance was taken out by the sponsor on 09/01/2014 under the number 137.681 with SHAM, in accordance with Article L 1121-10 of the Public Health Code (Appendix 12).

XV.4 APPLICATION TO CPP AND ANSM

This protocol received the favorable opinion of the PPC (Committee for the Protection of Persons) EST I on 17/04/2014 (Appendix 13).
This protocol received authorization from the ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé on 17/06/2014 (Appendix 14).

XV.5 COLLECTION OF THE PATIENT'S CONSENT

The investigator undertakes to collect, after information, the patient's clinical and biological consent in writing (information sheet and consent form in appendices 1 and 16). A copy of these consents must be kept by the investigator for 15 years. The originals must be given to the patient.

In accordance with the recommendations of the Cancer Plan (Measure 4.3.), these documents were submitted for review, advice and guidance to the Patients' Committee for Clinical Research (PCCR) of the National League Against Cancer.

XV.6 INFORMATION TO HOSPITAL MANAGEMENT AND RESEARCH AGREEMENT

Prior to the implementation of the study, the hospital management will be informed by the Sponsor of the investigator's interest in participating in this trial.
A no-cost research agreement will be established between the investigating center administrator and the sponsor.

XV.7 DATA ARCHIVING

The files will remain confidential and can only be consulted under the responsibility of the doctors in charge of the patients. The sponsor and the health authorities in case of inspection will have direct access to these documents.
At the end of the trial, the observation book will be kept for 15 years by the investigator.

XV.8 IT SUPPORT

In accordance with the text of the law n° 78-17 of January 6, 1978 modified by the law of August 9, 2004, relating to data processing, files and freedoms, the data of the trial will be recorded in a data bank of the Center of Randomization and Management Analysis of the FFCD, with the exception of the elements relating to the identity of the patients.

XV.9 DATA PROCESSING

The FFCD's Center for Randomization Management and Analysis (CRGA) will be responsible for data management and analysis.

XV.10 MONITORING, QUALITY ASSURANCE AND INSPECTIONS BY AUTHORITIES

The investigator agrees in advance that the records of the patients included in the trial may be consulted by a person mandated by the FFCD and/or by the health authorities to carry out an audit. On-site monitoring of records, scheduled after agreement with the investigator, may take place during and after the trial inclusion period.
This protocol will be monitored by the FFCD's mobile ARCs.

The investigator agrees to sign the observation books at the end of each visit.

XVI. PUBLICATION

The current FFCD publication rules will be applied (Appendix 11)

XVII. APPENDICES