Lipiodol as an imaging biomarker of tumor necrosis after transcatheter chemoembolization therapy in patients with primary and metastatic liver cancer

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Lipiodol as an imaging biomarker of tumor necrosis after transcatheter chemoembolization therapy in patients with primary and metastatic liver cancer

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Study Phase: II

Study Products: Lipiodol

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Protocol Sponsor

PI sponsored, Todd Schlachter, MD

Confidential Information

Protocol Revision Record

Final: January 28, 2013
Revised: Amendment 1, November 13, 2013
Amendment 2, May 28, 2015
Amendment 3, December 14, 2015

Table of Contents

Investigator Agreement Page

Study Title:

I confirm agreement to conduct the study in compliance with the protocol and all applicable regulations.

Investigator Name: _____

Affiliation: _____

Investigator Signature: _____ Date: _____

Schedule of changes (5/8/2017)

- Change of PI from Dr. Jean-Francois Geschwind to Dr. Todd Schlachter.

Schedule of changes (4/12/2016)

Page 29

- Added exclusion criteria: contraindication in areas where bile ducts are dilated, unless external biliary drainage is performed prior to injection.

Schedule of changes (12/14/2015)

Page 1

- Removed Johns Hopkins site
- Personnel changes: added Hyun Kim, MD, Teresa White, RN, Fangyong Li, MPH
- Removed: Ihab Kamel, MD PhD, Timothy Pawlik, MD PhD, Diane Reyes, CRNP, Robert Anders, MD PhD, Laura Wood, MD PhD, Sydney Carr, Taylor Dunklin, BS

Page 2

- Removed Johns Hopkins site

Page 13, 49 - 51

- Development of statistical designs

Page 52

- Updated monitoring plan

Schedule of changes (5/28/2015)

Page 1

- Added PI information for Yale School of Medicine site
- Added Robert Anders, MD PhD, Laura Wood, MD PhD, Eliot Funai, BS, Taylor Dunklin, BS.
- Removed Rafael Duran, MD, Richard Wahl, MD, Charlene Ofosu, MS, Elizaveta Besova.

Page 2

- Added address for where research will be conducted, Yale School of Medicine
- Added address for Yale SOM IRB

Throughout

- Amended the duration of follow-up, from 4 years to 6 months after TACE of targeted lesion is complete. Objective 2, which was to characterize lipiodol as a biomarker of survival, was amended to 'assess 6-month survival following therapy with lipiodol TACE'. The rationale is that patients are typically followed for response for 6 months after therapy and then are followed for survival, as standard of care, therefore the protocol follow-up is mirroring clinical practice.

Schedule of changes (11/13/2013)

Page 1

- Added Rafael Duran, MD and Todd Schlachter, MD to list of Investigators
- Added Elizaveta Besova

Page 2

- Formatting- removed nonapplicable information about coordinating centers
- Reformatted "Protocol Revision Record" for clarification. Removed protocol revisions prior to IRB approval

Page 6

- Corrected Sponsor section. Removed "Guerbet". Inserted "PI sponsored".
- Added Rafael Duran, MD and Todd Schlachter, MD to list of Investigators
- *Methodology*: Removed the term "unresectable". See changes below for page 24 for complete explanation.
- *Methodology*: Removed FDG-PET/CT of the liver at 1 month post completion of TACE. This is incorrect and is in several places throughout the protocol (pages 6, 7, 26, 27, 32). As correctly described (page 28, Section 5.3; page 30, section 5.3; page 39, Section 7.1) patients will have FDG-PET/CT at baseline, 3, and 6 months post completion of TACE.
- *Methodology*: Added that if the baseline FDG-PET/CT shows the index lesion is not PET avid, f/u FDG-PET/CT scans are omitted. (Addition also made on page 26, Section 5.1; page 30, Section 5.3)

Page 7

- *Inclusion criteria*: clarified patient population. See description below for Section 3.1 for explanation.

- *Duration of treatment*: clarified to describe expected duration enrollment, duration of treatment, and duration of follow-up

Page 20

Section 1.5.2, Safety/Adverse Events

- Added risk of allergic reaction

Page 23

Section 3, Subject Selection.

- Clarified that patients with HCC must meet either criteria:
  1) histological or cytological diagnosis, or
  2) the EASL criteria (the radiological presence of a liver mass greater than 2 cm, with arterial hypervascularity that is seen on two imaging modalities, within a cirrhotic liver, and in the presence of an alphafetoprotein (AFP) > 200 ng.mL will be used as an alternative diagnostic criterion)

Page 24

Section 3.1 Inclusion Criteria:

- Removed the term "unresectable". This is incorrect and is in several places throughout the protocol (pages 6, 23, 26, 31, . As correctly described (page 22, section 2.2.1; page 44, section 9.1.1 , page 26, Section 5.1)patients with HCC, who are referred for cTACE may be enrolled. Therefore, patients who are being worked up for transplant, listed for transplant, or who may undergo resection in the future, but who are currently referred for cTACE, may be enrolled. This is clear in on page 44, Section 9.1.1, where we describe that should patient undergo surgery, we will obtain tissue to correlate with imaging findings.

Page 26

Section 5.1 Overall Design

- Added Gadavist (gadobuterol) and Eovist (gadoxetate) to the list of contrast agents that may be used for the MRI scanning.

Page 27

Section 5.1 Overall Design

- Added clarification that all study imaging exams are read and interpreted by radiologists in the same manner as non-study clinical imaging studies. Added clarification that all study imaging

exams are interpreted by the study investigators in order to complete the objectives in Section 7 (Measurement of Effect) and Section 9 (Statistical Methods).

Section 5.2 Agent Administration

- Clarified the standard of practice method of agent administration for cTACE. The amounts of The amounts of chemoembolization material, lidocaine, and embospheres delivered are approximately:
    - 10 cc's of lipiodol,
    - 10 cc of chemotherapy, with 50 mg Doxorubicin and 10 mg of Mitomycin-C mixed 1:1 with Lipiodol (10 cc's) giving a total of 20 cc,
    - 10 cc of 1% lidocaine, and
    - 1 vial of embospheres measuring 100-300 microns

  However exact amounts are titrated to each clinical situation.

- "As in our standard of care practice, *approximately* 10 cc's of lipiodol is administered to the patients during a TACE procedure. The chemoembolization material consists of 10 cc of chemotherapy, with 50 mg Doxorubicin and 10 mg of Mitomycin-C mixed 1:1 with Lipiodol (10 cc's) giving a total of 20 cc. *The amount of chemoembolization material administered is titrated to the area being treated, i.e., a smaller area (lesion) may be adequately treated with a portion of the prepared chemoembolization material.*

  Due to the drug shortages, cisplatin has been unavailable for approximately the last 9 months.

  Therefore, currently, the chemoembolization agents consist of:

  - ***approximately*** 50 mg doxorubicin and 10 mg of mitomycin-C.

  In the event that cisplatin becomes available again, the chemoembolization agents would consist of:

  - ***approximately*** 50 mg doxorubicin, 10 mg of mitomycin-C, and 100 mg cisplatin

  To follow the chemoembolization materials, ***approximately*** 10 cc of 1% lidocaine and ***approximately*** 1 vial of embospheres measuring 100-300 microns, are administered. ***The amount of 1% lidocaine and of embospheres is titrated to each clinical situation.***

Page 27

- Administrative correction

Section 5.2.2 Regimen Description.

- Clarified to refer the reader back to Section 5.2 which has the identical information.

Page 30

Study calendar

- Formatting changes.

Page 31

Study calendar

- Corrected study calendar. Removed PET Scan at day 30

Page 33

Section 5.7 Criteria for Removal from Study

- For clarification, combined 2 criteria that were overlapping “removal at request of patient and representative” and “withdrawal of consent”

Page 36

Section 6.3.2.2.1

- Typo correction

Page 38

Section 6.3.3.3 Pregnancy

- Removed the phase “including at least 6 half lives after product administration” because the half-life of lipiodol is unknown.

Schema/Synopsis

Name of Sponsor/Company: PI sponsored		
Name of Finished Product: Lipiodol		
Name of Active Ingredient: Lipiodol		

Title of Study:
Lipiodol as an imaging biomarker of tumor necrosis after transcatheter chemoembolization therapy in patients with primary and metastatic liver cancer

Investigators:
Hyun Kim, MD, Todd Schlachter, MD, Julius Chapiro, MD

Study Center:
Yale University

Anticipated Study Period (years):	**Phase of Development:**
6 years- November 1, 2012-October 31, 2018	II

Objective:

To determine if Lipiodol can be used as an imaging biomarker of tumor necrosis after transarterial chemoembolization therapy in patients with primary and metastatic liver cancer.

Methodology:

The study is designed to treat patients with liver-predominant HCC or metastatic disease meeting study entry criteria. Patients will be treated with conventional, Lipiodol based chemoembolization on Day 0. If multiple TACE procedures are required, then the time points below will begin after the treatment is complete for a particular lesion in the liver.

The following imaging will be performed after the procedure:

1. Non-enhanced CT of the abdomen 24 hours after TACE and before surgical resection or transplantation if applicable.
2. DCE (dynamic contrast enhanced) - and diffusion-MRI of the liver before TACE, 1, 3, and 6 months post completion of TACE.
3. CT scan of the abdomen, with and without contrast, before TACE, 1, 3, and 6 months post completion of TACE.
4. FDG-PET/CT of the liver before TACE, 3 and 6 months post completion of TACE.
   *No F/U FDG-PET/CT if lesion is not avid

Timeline:

- Before TACE – DCE MRI + CT abdomen with contrast + PET-CT
- Day 0 – TACE
- Day 1 – Non-contrast CT of the liver

- Day 30 – DCE MRI + CT abdomen with and without contrast
- Day 90 – DCE MRI + CT abdomen with and without contrast + PET-CT
- Day 180 -- DCE MRI + CT abdomen with and without contrast + PET-CT
-

# of Patients:
60 (HCC (n=30) and metastatic disease (n=30)) to be enrolled; 100 patients total will be consented

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Hepatocellular carcinoma (HCC). Patients with liver-predominant disease, who have been referred for cTACE. Multifocal HCC is acceptable, no diffuse HCC. Or patients with a diagnosis of hepatic metastases from any solid tumor.

- Age $\geq$ 18
- ECOG performance status of 0-2.
- Childs class of A or B (up to 9)

Test product, dose and mode of administration, batch number:

Lipiodol . In TACE procedures, an emulsion is formed by mixing Lipiodol with the cytostatic drug(s) and is injected intra-arterially through the hepatic artery to produce avascularity and infarction/necrosis of the tumor(s).

Duration of enrollment: approximately 2 years

Duration of treatment: until investigator determines the lesion has been fully treated

Duration of follow-up: 6 months following completion of TACE

Criteria for evaluation:

Efficacy:

Response to contrast enhanced MRI will be assessed for measurable disease. For the purposes of this study, patients will be evaluated approximately 1, 3, and 6 months (Days 30, 90, and 180) following the last TACE (after the operator determines that a lesion has been fully treated).

Survival:

6-month survival will be assessed.

Statistical methods:

This is a trial evaluating Lipiodol as an imaging biomarker for successful treatment. A sample size of 60 (HCC (n=30) and metastatic disease (n=30)) will allow for data collection and analysis to assess Lipiodol as an imaging biomarker in this pilot study.

Objective 1: Explore whether Lipiodol can be used as an imaging biomarker predicting tumor response to therapy.

Lipiodol deposition will be measured as scores from 1 to 100 and (on the 24h non-contrast CT) will be also categorized by 4 ordinal levels: ≤25%, >25-50%, >50-75%, >75%.

Percent lipiodol deposition in the tumor (obtained from non-contrast CT) will be correlated with RECIST response separately using contrast CT, MRI and PET imaging. The Spearman's rank correlation coefficient will be used with RECIST response categories (CR, PR, SD, PD), and Pearson's correlation coefficient will be used for the % change in the sum of the longest diameter of target lesions (reference is baseline). The strategy is to assess which of the imaging modalities correlate most closely with lipiodol deposition.

Correlation of lipiodol deposition with other MR imaging methods

Percent lipiodol deposition (on the non-contrast CT) will be correlated with MRI response utilizing the EASL and qEASL amendment (necrosis).

Exact percent of lipiodol deposition (on the non-contrast CT) will be correlated with apparent diffusion coefficient (ADC) and with volumetic response using Pearson's product-moment correlation.

Objective 2: To assess 6-month survival following therapy with lipiodol TACE. Survival will be analyzed by using the Kaplan-Meier method to compare the progression free survival across the 4 ordinal Lipiodol retention strata.

List of Tables

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
CT	Computed tomography
MR	Magnetic resonance
PET	Positron emission tomography
ECOG	Eastern cooperative group
DCE-MRI	Dynamic contrast enhanced MRI
EASL	European Association for the Study of the Liver criteria

1. Introduction

1.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and represents more than 5% of all cancers. Approximately 500,000 cases of HCC are diagnosed each year and it is the third cause of cancer-related deaths [1-3]. There are wide geographical variations in the incidence of the disease with the highest rates in the developing countries of Asia and Africa. However, the incidence of HCC is increasing in North America and Europe [4].

Untreated HCC carries a poor prognosis and is directly related to degree of underlying cirrhosis and tumor stage. Early detection offers the only possibility for cure. Patient survival is generally not more than 6 months in patients with large tumor mass and advanced cirrhosis. Patients with small HCCs (< 5cm diameter) and stable liver function have a better prognosis with 2-year survival rates of 56% [5].

HCC is now responsible for 14,000 deaths annually in the United States. It is generally accepted that surgical resection, liver transplantation and percutaneous ablation are the only curative treatments for patients with early stage HCC. The shortage of donor livers further diminishes liver transplantation as a viable option for many patients. The majority of HCC patients (approx 85-90%) are not candidates for curative treatments either due to poor liver function or the presence of advanced disease. These patients are treated with palliative treatments.

Chemotherapeutic agents (eg. doxorubicin) can be infused directly into the systemic circulation but patients who receive this treatment suffer serious side effects that may be life threatening (eg cardiac toxicity), pain, nausea, vomiting, myelosuppresion and alopecia. For those patients able to receive systemic chemotherapy, response rates ranged from 15% to 20% and have had virtually no impact on survival.

These factors, combined with local pattern of disease dissemination, have made local interventional therapy the cornerstone of hepatocellular carcinoma treatment for unresectable disease and patients who are not eligible for transplant.

1.2. Hepatic Metastases from Solid Tumors

There are many solid-organ malignant tumors (colorectal carcinoma, neuroendocrine tumors, pancreatic endocrine tumors and other, non-colorectal non-neuroendocrine tumors) for which cure is not possible with current systemic agents. Many of these tumors are found to have already metastasized to the liver at the time of diagnosis or eventually metastasize to the liver despite best therapeutic efforts with

available systemic agents. The liver is the most common site of metastases from colorectal carcinoma and is a frequent metastatic site for pancreatic endocrine tumors (PET), neuroendocrine tumors (NET) and other tumor types. Overall, the largest risk factor for the development of hepatic metastases is the stage of the primary tumor (colorectal carcinoma) or the size of the primary tumor (NET, PET). In hepatic metastatic disease, the most important prognostic factor is the percent of liver replaced by tumor. If allowed to grow and disseminate within the liver, metastatic deposits become the dominant, and often, the most life-threatening feature of the metastatic disease, either through progressive hepatic failure or production of excess endocrine products that produce potentially lethal systemic consequences (NET, PET).

Due to the relative sensitivity of the liver to radiation, external beam radiation has had limited utility in treating hepatic metastatic disease. Modest improvements have been achieved in the treatment of metastatic colorectal cancer using new combination regimens of systemic agents; however, most patients ultimately fail first-line therapy either based on lack of efficacy or inability to tolerate further courses of treatment. A number of new, non-radiation based liver-directed therapies have been developed for reducing or controlling tumor mass in the liver that have demonstrated varying efficacy and patient tolerance. These treatments also may produce serious morbidity that adversely impacts patient quality of life, and can result in life-threatening complications and adverse events.

In summary, the status of clinical management of patients with metastatic disease involving the liver has experienced modest improvements over the past 40 years. Standardization of treatment approach has been hampered by the need to adapt therapy to tumor type and presentation, initial response to first line therapy and patient tolerance for therapeutic interventions. Diverse drugs, biologics, medical devices and surgical procedures are available for treatment of hepatic metastases. There is a clinical need to develop new, liver-directed therapies with less morbidity and improved patient tolerance compared with existing therapies. In addition, new therapies are needed that can be applied at any time in the ongoing course of treatment for a patient with metastatic liver disease.

1.3. Transarterial Chemoembolization for Hepatocellular Carcinoma and Metastatic Disease

Liver directed forms of therapy have become the mainstay of therapy of patients with unresectable HCC. These therapies include chemical (alcohol, acetic acid) and thermal (radiofrequency ablation, microwave, laser, etc) ablative techniques, as well as intra-arterial chemotherapy treatments. Intra-arterial therapies have been developed to take advantage of the fact that the hepatic artery supplies most of the blood flow and nutrients to hepatic tumors.

Of those, transcatheter arterial chemoembolization (TACE) is the most widely performed procedure for patients with unresectable HCC.Transarterial chemoembolization (TACE) involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic arteries feeding a liver tumor, thus combining chemotherapy administration with intra-tumor ischemia. The rational for TACE is that the infusion of drugs such as doxorubicin, mitomycin c and cisplatin suspended in an oily medium followed by embolization of the blood vessel with embolic agents will reduce arterial blood supply to the tumor allowing greater delivery of the chemotherapy to the tumor and thus causing necrosis of the tumor. Lipiodol is the most common vehicle used for the intra-arterial administration of the chemotherapeutic agents. The advantage of TACE is that higher concentrations of the drug can be delivered to the tumor with decreased systemic exposure compared with systemic chemotherapy. TACE has been shown to deliver up to 400 times the intra-hepatic concentration of chemotherapy in comparison to intravenous administration depending on the chemotherapeutic agent [6]. As such, tissue levels of chemotherapy within the tumor were found to be 40 times of that found in surrounding normal hepatic tissue. Embolization of a branch of the hepatic artery after the administration of chemotherapy results in the detection of the chemotherapeutic agent within the tumor of upwards of several months post administraton [7-9].

TACE achieves partial response in 15 – 55% of patients [10-16] and significantly delays tumor progression and vascular invasion [12, 16]. Recently two studies have reported survival benefits for chemoembolization in selected patients [16, 17]. The best candidates for chemoembolization are those with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread.

Currently, there are no randomized clinical trials demonstrating the superiority of any one chemotherapeutic agent; thus, any of the following agents are currently being used: doxorubicin, cisplatin, 5-fluorouracil (5-FU) or 5-fluorodeoxyuridine (5-FUDR) [5, 10, 11]. Embospheres® is usually used as the embolic material.

The impact of TACE on survival has been assessed through numerous prospective and retrospective studies. Two recently published randomized prospective clinical trials have shown a statistically significant survival advantage for TACE compared to symptomatic treatment. The first trial, which utilized cisplatin, Lipiodol, and gelatin sponge particles in 80 Asian patients, showed one-, two- and three-year survival rates of 57%, 31%, and 26% in treated patients compared to 32%, 11%, and 3% (respectively) in control patients treated with best available supportive care, giving a relative risk of

death of 0.49 (CI, 0.29 – 0.81)[18]. A second trial performed in Europe also showed a survival benefit in highly selected patients using Lipiodol, doxorubicin, and gel foam [15]. A recent meta-analysis confirmed the findings of the two randomized trials published by Llovet and Lo and showed that chemoembolization provides significant survival benefit in a selected group of patients, namely those with good performance status [14]. Based on those and other studies, chemoembolization is currently the standard of care for patients with intermediate stage HCC and has been included since 2006 as part of the official guidelines for the treatment of patients with HCC (by the American Association for the Study of Liver Diseases (AASLD), as well the National Cancer Care Network (NCCN) and European Association of the Study of the Liver (EASL).

TACE has also been used with success in secondary unresectable hepatic malignancies.

1.3.1. Colorectal Metastases

The only chance of cure for patients with liver metastases from colon carcinoma is resection. Unfortunately, fewer than 30% of patients have resectable disease [19]. Even in optimal resection candidates, recurrence is frequent, with a 5-year survival rate of only 35%. Negative predictors of survival include a short interval between diagnosis of the colonic primary tumor and the liver metastases, number of metastases, carcinoembryonic antigen level greater than 10 ng/mL, extrahepatic disease, and the ability to obtain a negative resection margin [20].

The majority of patients with hepatic metastases from colon cancer undergo systemic chemotherapy. There are a variety of novel chemotherapeutic agents are being used to treat metastatic colorectal cancer. Cytotoxic agents such as irinotecan and oxaliplatin, as well as the monoclonal antibodies cetuximab and bevacizumab, have shown promising results in early trials. Combination therapy with bevacizumab in addition to irinotecan, 5-fluorouracil, and leucovorin has improved survival to a mean of 20.3 months [21]. Similar survival was identified with addition of oxaliplatin to 5-fluorouracil and leucovorin [22] However, even with these agents, progressive disease, particularly in the liver, occurs at a mean of 9–10 months. At this point, palliative therapies such as chemoembolization are considered.

Phase II studies of chemoembolization for metastatic colorectal cancer have been reported by several centers in the United States. Patients enrolled in these trials are usually individuals in whom systemic and/or intraarterial infusion chemotherapy has failed. Abramson et al [23] devised a spreadsheet model to determine cost-effectiveness thresholds for palliative chemoembolization for colorectal metastases. A mean survival time of 12 months or greater was demonstrated to be necessary for chemoembolization to be considered a cost-effective method of treatment. Lang et al [24] used a

combination of superselective segmental and selective lobar injections of a doxorubicin/iodized oil emulsion in the treatment of 46 patients. The actuarial survival rates were 68% at 1 year and 37% at 2 years. In the study of Sanz-Altamira et al [25], 40 patients received chemoembolization with 5-fluorouracil, mitomycin-c, iodized oil, and gelatin sponge. The median survival time after the first chemoembolization procedure was 10 months. A number of prognostic factors predictive of longer survival were identified. Patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 had a median survival of 24 months, versus 3 months among patients with a performance status of 2. Patients with extrahepatic disease at the time of initial chemoembolization had a median survival of 3 months, versus 14 months for those with isolated liver metastases. Among patients with good performance status and no extrahepatic disease, the survival rates were 73% at 1 year and 61% at 2 years after chemoembolization. In the study of Tellez et al [26], 30 patients underwent chemoembolization with cisplatin, doxorubicin, mitomycin-c, and bovine collagen. Median survival times were 8.6 months from first chemoembolization and 29 months from diagnosis. In a study by Soulen [27], 51 patients underwent chemoembolization with cisplatin, doxorubicin, mitomycin- c, iodized oil, and polyvinyl alcohol. Actuarial survival rates from diagnosis with liver metastases were 86%, 55%, and 23% at 1, 2, and 3 years, with a median of 24 months. Outcomes in patients with isolated liver metastases who were treated with chemoembolization by Salman et al [28] were similarly encouraging, with a mean survival time of 15 months versus 8 months among patients with extra-hepatic disease. The results in these extensively pretreated patients are promising, but high early response rates do not necessarily cause an improvement in survival. A consistent trend toward survival times longer than 12 months after initial therapy has also been demonstrated, suggesting that chemoembolization for colorectal metastases is a cost-effective method of treatment for patients with good performance status and disease isolated to the liver.

1.3.2. Ocular Melanoma

The liver is the initial site of metastatic disease in approximately 50% of patients with ocular melanoma [29]. More than 90% of patients with metastatic ocular melanoma will develop liver metastases[30]. When liver metastases develop, involvement is rapidly widespread and aggressive, with median survival times of 2–6 months [29]. A review of a variety of treatment methodologies in 201 patients by Bedikian et al [31] demonstrated longer survival with chemoembolization versus any other treatment method, including intraarterial and systemic chemotherapy, leading the authors to state that patients with isolated liver metastases from ocular melanoma should undergo hepatic arterial chemoembolization as

a primary therapy. Mavligit et al [32]reported 30 patients treated by serial chemoembolization with cisplatin and polyvinyl alcohol particles. There was one complete response at follow-up imaging, and 46% of patients had a partial response (50% tumor destruction at follow-up imaging). Median survival time was 11 months (14 months for patients whose disease responded vs 6 months those who showed no response), with an actuarial survival rate of approximately 33% at 1 year.

1.3.3. Neuroendocrine Tumors

Embolization has an established role in the palliation of these hypervascular tumors and typically produces symptom-free intervals in 90%–100% of patients. Two reports that initially evaluated chemoembolization of neuroendocrine tumors [33, 34] found a duration of response after chemoembolization of nearly 2 years. Brown et al [35] described objective responses in 96% of patients treated with hepatic arterial embolization without chemotherapy. Treatment for pain as the primary indication had less-durable results (6.2 months) than when embolization was performed for hormonal symptoms with or without the presence of pain (16 –17.5 months). Gupta et al [36] reported outcomes in 81 patients treated with embolization alone (*n* _=50) or chemoembolization (*n* =31). The time to symptomatic progression after arterial therapy was 19 months and the mean survival time for the patient group was 31 months.

1.3.4. Sarcoma

Mavligit et al [37] reported major regression of metastatic leiomyosarcoma in 10 of 14 patients treated with cisplatin/ gelatin sponge chemoembolization followed by a 2-hour vinblastine infusion into the hepatic artery, with a median duration of response of 1 year. Disease in 10 of 16 patients treated with cisplatin, doxorubicin, mitomycin-c, iodized oil, and polyvinyl alcohol particles by Rajan et al [38] showed a response, with extensive tumor necrosis on computed tomography in all cases. Three patients became candidates for surgical resection after treatment. Because systemic chemo-therapy and radiation therapy are ineffective against metastatic sarcomas in the liver, chemoembolization appears to be the most effective treatment for unresectable disease.

1.3.5. Cholangiocarcinoma

Burger et al [39] reported a median survival of 23 months after chemoembolization in 17 patients with unresectable cholangiocarcinoma. Two patients had their disease down-staged enough after chemoembolization to become resectable. Historic survival for patients with unresectable cholangiocarcinoma is 5–8 months. Even candidates for surgical resection have limited survival rates of

20%–56% at 3 years. Complication rates for this group [39] were in keeping with those for treatment of other tumor types. Chemoembolization appears to be a viable treatment option for well-compensated patients with unresectable cholangiocarcinoma.

1.3.6. Other Metastases

Liver metastases from lung, breast, pancreas, stomach, small bowel, kidney, bladder, thymus, ovary, or thyroid tumors, as well as those from unknown primary tumors, have been treated with chemoembolization [40-42]. The published reports lump together patients with different tumor types, making interpretation of the results difficult. Overall, mixed metastatic lesions treated with chemoembolization are associated with a 60%–75% objective response rate and median patient survival times of 8–11 months.

1.4. Transarterial Chemoembolization Safety Profile

Generally, TACE is a well tolerated procedure, although side effects are common. Embolization of the liver has been performed for decades for a variety of indications and is well-tolerated. Embolization of solid organs causes a self-limited post-embolization syndrome in the majority of patients, consisting of varying degrees of pain, nausea, vomiting, and fever. This is independent of chemotherapeutic drug use, reason for embolization (eg, bleeding, tumor), and the organ treated (eg, liver, kidney, spleen, uterus). With current medical care (eg, hydration, antiemetic therapy, and pain control), post-embolization syndrome is well-tolerated, and 50% of patients can be discharged from the hospital the day after chemoembolization. The average length of stay is 1.5 days. Liver function is transiently affected with an increase in liver aminotransferase levels. These values usually peak 3–5 days after therapy and return to baseline levels by 10 –14 days after embolization. There is no sustained degradation of liver function in properly selected patients who do not meet the well-established exclusion criteria for hepatic artery occlusion, even in the presence of cirrhosis [43]. Because most of the injected drug is retained in the liver, systemic toxicity is minimized, with little bone marrow suppression. The cumulative toxicity is far more limited than is experienced with systemic chemo-therapy, which requires protracted drug exposure for an indefinite period of time. Treatment related complications occur in approximately 10% of performed procedures, with mortality rate around 2% [44].

Serious adverse events occur after approximately 5% of chemoembolization procedures. The most common serious adverse events are liver abscess or liver infarction, which occur in approximately 2% of cases each. The 30-day mortality rate is 1% [45-47] [48].

Constitutional Symptoms. The postembolization syndrome consisting of transient abdominal pain, ileus, fever and malaise affects 60% to 80% of patients receiving TACE. Prophylactic antibiotics are not routinely administered as the fever is a predictor of treatment response. This fever is a result of tumor necrosis initiated by the therapy.

Gastrointestinal Side Effects and Complications. Transaminases commonly rise 10 fold. Patients may develop ischemic cholecystitis, hepatic abscess or biliary strictures. Additionally, a minority of patients will develop nausea/vomiting and ascites.

Endocrine Complications. Some patients may develop symptomatic hypothyroidism as a result of retained iodine load.

Hematologic Complications. Some patients may develop a leukemoid reaction. Bone marrow toxicity is uncommon occurring in less than 4% of patients and includes neutropenia and thrombocytopenia. A small cohort of patients has developed gastrointestinal hemorrhage as a result of TACE therapy.

1.5. Clinical Agent: Lipiodol (Ethiodol)

Product Name

Lipiodol® (ethyl esters of iodized fatty acids of poppy seed oil)

Manufacturer

Due to the current critical shortage of ETHIODOL®, Brand of Ethiodized Oil Injection, Guerbet is coordinating with the FDA to increase the availability of the ethyl esters of iodized fatty acids of poppy seed oil product. Guerbet has acquired the Ethiodol® NDA from Nycomed US Inc. effective May 7, 2010 and is working with the FDA to resume manufacturing of Ethiodol in the near future to ensure continued availability for the US patients. During this interim period, Guerbet, in conjunction with the FDA, is initiating a temporary importation of LIPIODOL® ULTRA-FLUIDE, ethyl esters of iodized fatty acids of poppy seed oil, to the United States market. LIPIODOL® ULTRA-FLUIDE contains the same drug components as ETHIODOL®, Brand of Ethiodized Oil Injection, (previously manufactured and marketed in the United States by Savage Laboratories, a subsidiary of Nycomed). LIPIODOL® ULTRA-FLUIDE is manufactured in compliance with European Good Manufacturing Practice (GMP) regulations by Delpharm Tours (France) for Guerbet.

At this time, no other entity except Guerbet is authorized by the FDA to import or distribute LIPIODOL® ULTRA-FLUIDE.

Chemical Name and Structure

Lipiodol is an X-ray contrast medium consisting of a preparation of ethyl esters of fatty acids, diiodized at C16 and C18. It is obtained from natural poppy seed oil which has undergone iodination and transesterification. The product is provided in the form of a solution for injection as a clear, pale yellow to amber solution packaged in 10 mL glass ampules. Lipiodol contains no excipients. Theiodine concentration of the preparation is 48 mg Iodine/mL.

Use of Ethiodol

In the United States, Lipiodol has been approved for use since 1954 and is labeled for use in patients undergoing hysterosalpingography or lymphography. Lipiodol is primarily used off-label in chemoembolization procedures for the treatment of primary and secondary hepatic malignancies, and in various embolization procedures. It is also used off-label for computed tomography of the liver and spleen, and to detect hepatic metastases.

Lipiodol is commonly used in arterial chemoembolization. Besides its opacifying properties, it acts as both an embolic agent and a carrier of chemotherapeutic agents to the tumor.

- When injected into the hepatic artery, Lipiodol remains preferentially in an HCC for several weeks to over 1 year, due to the hypervascularity of the tumor and an absence of Kupffer cells inside tumor tissues. This results in an embolic effect on small tumor vessels [49].
- In TACE, Lipiodol is used as a vehicle to carry and localized chemotherapeutic agents inside a tumor. When the Lipiodol and drug mixture is injected into a vessel supplying the tumor, the drug remains in high concentrations within the tumor for a prolonged period [49].
- Because Lipiodol is a contrast agent and remains within the tumor, the areas of treated tumor are easily identified using radiographic imaging**.**

In TACE procedures for HCC treatment, an emulsion is formed by mixing Lipiodol with the cytostatic drug and is injected intra-arterially through the hepatic artery to produce avascularity and infarction/necrosis of the tumor. Lipiodol has been found to remain selectively in the neovasculature and extravascular tissues of the HCC for very long periods. This technique also allows for targeted delivery of the cytostatic drug inside or close to the tumor and a prolonged intra-tumoral residence time secondary to the iodized oil, leading to a prolonged local action and reducing systemic effects of the cytostatic drug [50, 51]. As a whole, the therapeutic action of chemoembolization results from prolonged drug action and infarction [52]. Some authors have shown that tumor cytostatic drug

concentrations achieved this way are several thousand-fold higher than plasma drug concentrations [51]. In addition, during the process, the tumor is untouched from direct instrumentation or surgical manipulation that potentially may lead to tumor cell dissemination [50].

The efficacy of concomitant use of ethiodized oil and TACE procedures has been generally recognized for more than 2 decades.

1.5.1. Relevant Pre-clinical Information

Several carriers for the selective delivery of cytotoxic drugs to liver tumors have been investigated, amongst which Ethiodol is considered the agent of choice for this purpose as it is avidly taken up and retained for long periods of time by 85% of HCCs [51, 52]. Ethiodol selectively remains not only in large tumors but also in smaller intrahepatic metastases [35, 52]**.**

1.5.2. Safety/Adverse Events

Possible side effects of Lipiodol are transient fever post-procedure and gastrointestinal disorders (nausea, vomiting or diarrhea). In patients with an iodine deficiency, there is a risk of hyperthyroidism (symptoms include weight loss, accelerated heart rate, increased intestinal transit rate, anxiety, insomnia, etc.). Additionally, there is a risk of an allergic reaction. Patients with a history of allergic reactions to iodinated products are premedicated prior to a TACE procedure as per standard of care. Please see package insert in Appendix.

Lipiodol has been used since 1954 in general, and for the last 2 decades in TAE/TACE procedures, without any noted increase in risks or special complications. It can therefore be concluded that Lipiodol can be safely used in selective embolization.

1.6. Rationale

The goal of Lipiodol based TACE is to deliver highly concentrated doses of chemotherapy to the tumor in order to maximize tumor kill and minimize systemic release of the drug in the plasma thereby reducing side effects (vs chemotherapy). The key advantages of TACE are the precise nature of the delivery by utilizing the artery feeding the tumor thereby allowing the chemotherapy to be deposited directly within the tumor bed and the ability to achieve high concentrations of doxorubicin, cisplatin, mytomycin-c within the tumor bed. There are three established purposes of Lipiodol in the chemotherapy cocktail:

(1) the ability to see where the chemotherapy is being delivered during the procedure, (2) to provide an embolic effect to the feeding vessel of the tumor, and (3) to provide a vehicle for the chemotherapeutic agent.

However, despite over 25 years of clinical experience with lipiodol based TACE, the role of Lipiodol remains incompletely studied, especially its potential use as an imaging biomarker of tumor response.

We therefore propose to study the potential role of lipiodol as an imaging biomarker of tumor response. When Lipiodol is delivered to the tumor during TACE, it is generally retained within the tumor for many weeks to months. The radio-opacity of Lipiodol makes it very easy to track. If it is indeed proven true that Lipiodol retention in the treated tumor equates to tumor necrosis, then Lipiodol could potentially be considered as a valid imaging biomarker of successful tumor treatment. This hypothesis will be tested by imaging patients with multiple modalities (DCE-MRI, PET-CT, and CT) before and at multiple time points after TACE. The scans will be overlayed with each other (image fusion) and tumors will be compared from the standpoint of necrosis and viability.

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

- To determine whether Lipiodol can be used as a valid imaging biomarker of successful drug delivery to liver tumors and of tumor response to therapy.

2.1.2. Secondary Objective

- To estimate 6-month survival following therapy with lipiodol TACE.

2.2. Endpoints

2.2.1. Primary Endpoint

- RECIST/EASL/qEASL response, separately using contrast CT, MRI and PET, as an indicator of success of tumor response to therapy
    - RECIST/EASL/qEASL *response* will be based on the *percentage change from baseline* of the diameter of the specific target lesion identified at baseline (RECIST)/the percentage change in the viable tumor area of the specific target lesion identified at baseline (EASL). The response scale is 0-100% for decrease/ (opposite sign) 0-100% for increase.

RECIST/EASL/qEASL *response categories (CR, PR, SD, PD)*, will be based on the *percentage change from baseline* of the diameter of the specific target lesion identified at baseline (RECIST)/the percentage change in the viable tumor area/volume of the specific target lesion identified at baseline (EASL/qEASL). *The analytic strategy is to measure the association between baseline lipiodol deposition and the treatment responses indicated by the imaging modalities. Separate analyses may be performed for each measurement time point for the respective imaging modalities.*

2.2.2. Secondary Endpoint

- 6-month survival of patients with HCC and liver metastases treated with TACE utilizing Lipiodol.

The analytic strategy is to measure the association between baseline lipiodol deposition and the 6-month survival rate by estimating median survival for each stratum, and by testing for homogeneity using a logrank test (if hazards are proportional).

3. Subject Selection

HEPATOCELLULAR CARCINOMA

Patients must have:

a histological or cytological diagnosis (documentation of original biopsy for diagnosis is acceptable if tumor tissue is unavailable), or meet the EASL criteria (the radiological presence of a liver mass greater than 2 cm, with arterial hypervascularity that is seen on two imaging modalities, within a cirrhotic liver, and in the presence of an alphafetoprotein (AFP) > 200 ng.mL will be used as an alternative diagnostic criterion) for diagnosis of HCC

-HCC who are Childs class A or B (see Table below) with liver-predominant disease.

Child-Pugh Classification of Liver Disease Severity

	Points Assigned		
Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	>3
Albumin, G/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin Time			
Seconds over control	1-3	4-6	>6
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh Classification of Liver Disease Severity: Modified Child-Pugh classification of liver disease severity according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10 -15 is grade C (decompensate disease). These grades correlate with one-year and two-year percent survival; grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C - 45 and 35 percent, respectively.

HEPATIC METASTASES FROM ANY SOLID TUMOR

Patients with a diagnosis of hepatic metastases from any solid tumor must have histological or cytological diagnosis of the primary tumor.

3.1. Inclusion Criteria

3.1.1. Hepatocellular carcinoma (HCC) with liver-predominant disease, who have been referred for cTACE. Multifocal HCC is acceptable, no diffuse HCC. Or, patients with a diagnosis of hepatic metastases from any solid tumor.

3.1.2. Age $\geq$ 18

3.1.3. ECOG performance status of 0-2.

3.1.4. Childs class of A or B (up to 9)

3.2. Exclusion Criteria

3.2.1. Any contraindication to doxorubicin, cisplatin, or mitomycin-c administration (or specific mixture of chemotherapy drugs to be used)

3.2.2. Evidence of severe or uncontrolled systemic diseases.

3.2.3. Congestive cardiac failure >NYHA class 2, MI within 6 months, active coronary artery disease, cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin, unstable angina, or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial.

3.2.4. Known allergy to Lipiodol (Ethiodol), poppyseed oil, or iodinated contrast agents (that cannot be adequately mitigated with a pre-procedure medications)

3.2.5. Main portal vein thrombosis is excluded; segmental or branch portal vein thrombosis is acceptable

3.2.6. Patients who are breastfeeding

3.2.7. Patients who are pregnant

3.2.8. Contraindicated in areas of the liver where the bile ducts are dilated, unless external biliary drainage is performed before injection.

3.3. Inclusion of Woman and Minorities

All patients, irrespective of sex or ethnicity, will be sequentially invited to participate in the study until enrollment has been met.

4. Subject Registration Procedures

4.1. General Guidelines

Patients consented for the study will be entered into the Yale-New Haven Health electronic database (OnCore) and entered into the study enrollment log.

4.2. Registration Process

Patients enrolled into the study (treated with conventional TACE) will be given a study identifier and will be counted in the final data analysis.

4.3. Screening Assessments

Assessments completed in the initial clinic visits (pre-consent), as part of standard of care assessments, may be used a study screening assessments.

Evaluations are within 30 days prior to TACE. If clinically indicated, blood work will be repeated within 1 week of treatment.

- History and Physical exam (including vital signs, ECOG-PS assessment)
- Chemistry Panel
- AST, ALT, bilirubin(total and direct), alkaline phosphatase, total protein, albumin, calcium, glucose, creatinine, blood urea nitrogen (BUN), bicarbonate
- Electrolyte Panel
    - sodium, potassium, and chloride
- Complete Blood Count
    - hemoglobin, hematocrit, platelet count, white blood cell count (WBC). White blood cell count (WBC) should include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts.
- PT/INR
    - PT, the International Ratio of PT (PT-INR)
- Alpha Feto-Protein
- Serum or urine Pregnancy Test
    - for women of childbearing potential (must be negative)
- Cardiovascular: Electrocardiogram and NYHA classification if warranted
- CT with contrast of the chest-abdomen-pelvis
- Contrast enhanced MRI of the liver
- PET/CT

5. Study Design/Investigational Plan

5.1. Overall Design

The study is designed to treat patients with liver-predominant HCC or metastatic disease meeting study entry criteria. Patients will be treated with conventional, Lipiodol based chemoembolization on Day 0. If multiple TACE procedures are required, then the time points below will begin after the treatment is complete for a particular lesion in the liver.

The following imaging will be performed after the procedure:

- Non-enhanced CT of the abdomen 24 hours after TACE and **before surgical resection or transplantation if applicable**.
  - Non-enhanced CT of the abdomen 24 hours post TACE is performed to document deposition of the lipiodol into the targeted area of the liver.

- DCE (dynamic contrast enhanced) - and diffusion-MRI of the liver before TACE, 1, 3, and 6 months post completion of TACE.
  - MRI of the liver: contrast agent used is Magnevist (gadopentetate dimeglumine), Multihance (gadobenate dimeglumine), Gadavist (gadobuterol), or Eovist (gadoxetate). The administered dose for agents is 0.1 mmol/kg (0.2 mL/kg).
  - The MRI contrast agents are administered according to label.

- CT scan of the abdomen, with and without contrast, before TACE, 1, 3, and 6 months post completion of TACE.
  - CT of the abdomen: contrast agents used are Omnipaque (iohexol) or Visipaque (iodixanol). The administered dose for both agents is 120 cc's for patients weighing ≥ 120 lbs, and is 1cc/lb for patients weighing under 120 lbs.
  - The CT contrast agents are administered according to label.

- FDG-PET/CT of the liver before TACE, 3, and 6 months post completion of TACE.
  - The radioactive dose of FDG dose is based on patient weight, 0.09mci /lb(minimum 10mci, max 25mCi). The FDG is sourced from PETNET Solutions Inc., a subsidiary of Siemens Medical Solutions USA, Inc.
  - The FDG is administered as standard of care.

    *No F/U FDG-PET/CT if lesion is not avid

Timeline:

- Before TACE – DCE MRI + CT abdomen with contrast + PET-CT
- Day 0 – TACE
- Day 1 – Non-contrast CT of the liver
- Day 30 – DCE MRI + CT abdomen with and without contrast
- Day 90 – DCE MRI + CT abdomen with and without contrast + PET-CT
- Day 180 -- DCE MRI + CT abdomen with and without contrast + PET-CT

The study imaging exams listed above (MRI, CT, and PET) will be read and interpreted by radiologists in the same manner as non-study clinical imaging studies. In addition to the clinical reads, the study investigators will interpret the study imaging exams in order to complete the objectives in Section 7 (Measurement of Effect) and Section 9 (Statistical Methods).

5.2. Agent Administration

As in our standard of care practice:

The amounts of chemoembolization material, lidocaine, and embospheres delivered are approximately:

- 10 cc's of lipiodol,
- 10 cc of chemotherapy, with 50 mg Doxorubicin and 10 mg of Mitomycin-C mixed 1:1 with Lipiodol (10 cc's) giving a total of 20 cc,
- 10 cc of 1% lidocaine, and
- 1 vial of embospheres measuring 100-300 microns

However exact amounts are titrated to each clinical situation.

A*pproximately* 10 cc's of lipiodol is administered to the patients during a TACE procedure. The chemoembolization material consists of 10 cc of chemotherapy, with 50 mg Doxorubicin and 10 mg of Mitomycin-C mixed 1:1 with Lipiodol (10 cc's) giving a total of 20 cc. *The amount of chemoembolization material administered is titrated to the area being treated, i.e., a smaller area (lesion) may be adequately treated with a portion of the prepared chemoembolization material.*

Due to the drug shortages, cisplatin has been unavailable for approximately the last 9 months.

Therefore, currently, the chemoembolization agents consist of:

- ***approximately*** 50 mg doxorubicin and 10 mg of mitomycin-C.

In the event that cisplatin becomes available again, the chemoembolization agents would consist of:

- ***approximately*** 50 mg doxorubicin, 10 mg of mitomycin-C, and 100 mg cisplatin

To follow the chemoembolization materials, ***approximately*** 10 cc of 1% lidocaine and ***approximately*** 1 vial of embospheres measuring 100-300 microns, are administered. ***The amount of 1% lidocaine and of embospheres is titrated to each clinical situation.***

5.2.1. Dose Escalation

Not applicable

5.2.2. Regimen Description

See Section 5.2, Agent Administration.

5.3. Visit Schedule and Study Evaluations

EVALUATIONS IMMEDIATELY PRIOR TO TACE

- Documentation of vital signs (heart rate, blood pressure, and respirations)

EVALUATIONS IMMEDIATELY FOLLOWING TACE

- Documentation of vital signs (hear t rate, blood pressure, and respirations)

EVALUATIONS AFTER TACE

- Physical exam and review of systems after TACE, prior to post-procedure discharge to home

- Physical Exam, Blood pressure monitoring, Review of systems, Labs: 1 month after treatment, then 2 months after this, and 3 months after this (Days 30, 90, and 180)
- MRI: Day 30, 90, 180
- CT of abdomen with and without contrast: Day 30, 90, 180
- **PET-CT: Day 90, Day 180**
  *No F/U FDG-PET/CT if lesion is not avid

5.4. Concomitant medications

- Metformin: Patients being treated with metformin will have the metformin suspended 48 hours before the TACE procedure and restarted 2 days after the procedure.

- Diuretics: Patients being treated with diuretics will not have the diuretics held prior to TACE except when clinically indicated (when the patient is at increased risk for dehydration). This decision is at the discretion of the Investigator.

Please see the below Study Calendar table.

Table 1. Study Calendar

Parameter	Pre-treatment	Day 0	Day 1	Day 30 (+/- 7 d)	Day 90 (+/- 14 d)	Day 180 (+/- 21 days)
Informed consent[1]	X[1]					
Medical History	X[1]			X	X	X
Review of systems			X			
Physical Exam	X[1]		X	X	X	X
Performance Status	X[1]			X	X	X
Hematology[2]	X[1]			X	X	X
Chemistry/Electrolyte Panel[3]	X[1]			X	X	X
PT/INR	X[1]			X	X	X
Serum/urine pregnancy test	X[1]					
NYHA Classification	X[4]					
Electrocardiogram	X[4]					
CT (abdomen), w + w/o contrast	X[1]			X	X	X
Tumor Marker (AFP, CEA, Chromogranin A, or	X[1]			X		

other appropriate marker)					**X**	**X**
Concomitant Meds	**X**[1]			**X**	**X**	**X**
TACE Procedure		**X**[5]				
CT scan without contrast	**X**[1]		**X**			
MRI (liver)	**X**[1]			**X**	**X**	**X**
Pet-CT scan	**X**[1]				**X**	**X**

[1] Within 30 days prior to study enrollment
[2] Hemoglobin, hematocrit, platelets, WBC with differential
[3] Creatinine, BUN, total bilirubin, AST, ALT, alk. phos, Ca, K, Cr, Na, albumin, total protein.
[4] If indicated
[5] Repeated as indicated until physician determines that lesion has been fully treated
* Windows of 7, 14 and up to 21 days are allowed around the follow-up visits

5.5. Duration of Therapy

TACE is offered as indicated, per standard of care.

5.6. Duration of Follow-up

6 months from completion of TACE

5.7. Criteria for Removal from Study

Subjects who meet the following criteria should be discontinued from the study:

- At the request of the patient or a representative/ Withdrawal of consent
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, contribute to toxicity
- Deterioration of PS to ECOG 4
- The patient is lost to follow-up
- Death

5.8. Study Discontinuation

The investigator has the right to close the study, at any time, although this should occur only after consultation between involved parties. The Ethics Committee (EC)/Institutional Review Board (IRB) must be informed. Events that may trigger premature termination of a study include, but are not limited to: new toxicity finding, results of any interim analysis, completed accrual and follow-up of patients, non-compliance with the protocol, change in development plans for the study drug, slow recruitment, or poor quality data.

6. Adverse Event Collection and Reporting Requirements

6.1. Definitions

6.1.1. Adverse Event (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product (refer to ICH E6 GCP Guidance – section 1.2).

6.1.2. Serious Adverse Event (SAE)

A Serious AE (SAE) is any untoward medical occurrence that at any dose produces any of the following outcomes (refer to ICH E6 GCP Guidance – section 1.50):

- Results in death;
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below for exceptions);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form);
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

NOTE:

The following hospitalizations are not considered SAEs:

- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases;
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.3. Non-serious Adverse Event

A non-serious adverse event is any adverse events not classified as serious (as described in previous section).

6.2. Adverse Event Coding

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
- **Attribution of the AE:**
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

6.3. Adverse Event Capture and Reporting

6.3.1. Routine Adverse Event Capture and Reporting

The collection of all AE information begins at initiation of investigational product and continues during the clinical study until 30 days of receiving the last TACE on study.

Because Lipiodol based TACE is known to be safe and has been used effectively for over 20 years, targeted data collection is appropriate.

Adverse event data that will be collected and reported:

- All serious adverse events, deaths, and events that lead to study discontinuation
- Unscheduled hospitalizations
- Grade 3 and 4 adverse events, as well as Grade 2 events that affect vital organs (heart, liver)
- Data for all subject withdrawals

Adverse events should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified AEs must be recorded and described on the appropriate AE page of the Case Report Form (CRF).

6.3.2. Serious Adverse Event Capture and Reporting

ALL serious adverse events, regardless of causality must be reported to the following entities:

- IND Sponsor
- IRB (per the IRB's reporting requirements)
- FDA (if PI is also the sponsor of the IND/IDE)

6.3.2.1. SAE Reporting to the IRB

SAEs that meet the IRB's definition of an unanticipated event per Yale IRB Policy 710 must be reported to the IRB (Yale IRB Policy 710).

6.3.2.2. Sponsor SAE Reporting to the FDA (for Sponsor-Investigator INDs)

All SAEs are reported to the FDA via the IND annual report per 21 CFR 312.33. SAEs deemed unexpected and related to the investigational product qualify for expedited reporting and must be submitted by the IND Sponsor-Investigator to the FDA per 21 CFR 312.32 as shown immediately below.

6.3.2.2.1. 7 Calendar-Day Telephone or Fax IND Safety Report to FDA

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Sponsor Investigator to be possibly related to the use of Lipiodol within 7 calendar-days of first learning of the event. An unexpected adverse event deemed possibly related to the use of an investigational study drug is defined as any adverse drug experience of which the specificity or severity is not consistent with the current investigator brochure, the general investigational plan, or elsewhere in the current application, as amended.

Such reports are to be telephoned or faxed to the FDA within 7 calendar-days of first learning of the event. Each telephone call or fax transmission should be directed to the FDA department that is responsible for the review of the IND.

6.3.2.2.2. 15 Calendar-Day Written IND Safety Report to FDA

The Sponsor-Investigator is required to notify the FDA, and all participating investigators (as applicable), in a written IND Safety Report, of any serious, unexpected adverse event considered by the Sponsor-Investigator to be possibly related to the use of Lipiodol within 15 calendar-days of first learning of the event.

A serious, unexpected adverse event deemed possibly related to the use of an investigational study drug is any adverse drug experience of which the specificity or severity is not consistent with the current investigator brochure, the general investigational plan, or elsewhere in the current application, as amended, and results in any of the following outcomes:

- Death (report first as a 7-day telephone/fax report);
- life-threatening adverse drug experience (report first as a 7-day telephone/fax report);
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity, or a congenital anomaly/birth defect;
- or is an important medical event that may not result in death, be life-threatening, or require hospitalization but is considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All written IND Safety Reports should include an Analysis of Similar Events in accordance with 21 CFR 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports and be submitted to the FDA, within 15 calendar-days of first learning of the event. The FDA prefers these reports be documented on a MedWatch 3500A Form, but alternative formats are acceptable (e.g., summary letter).

6.3.2.2.3. Follow-up Reports to FDA

All follow-up information concerning IND Safety Reports should be submitted to the FDA as soon as possible (and no later than 15 calendar days after receiving an FDA request for more information).

6.3.3. Other Potential Adverse Events

6.3.3.1. Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF. In addition, the following laboratory abnormalities should also be captured on the non-serious AE CRF page or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory abnormality that required the subject to have Lipiodol discontinued or interrupted;
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

6.3.3.2. Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

6.3.3.3. Pregnancy

Sexually active women of child bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative serum pregnancy test 7 days prior to receiving investigational product. All WOCBP should be instructed to contact the investigator immediately if they suspect they may be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational product exposure, the investigational product will be permanently discontinued in an appropriate manner. Exceptions to the investigational product discontinuation may be considered for life-threatening conditions only after consultation with the sponsor or as otherwise specified in this protocol. The investigator must immediately notify the sponsor of this event, record the pregnancy on the SAE form. Initial information

on a pregnancy must be reported immediately to the sponsor and the outcome information provided once the outcome is known. Forward these forms to the sponsor according to SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-rays studies). Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

6.3.3.4. Other Safety Considerations

Any significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by protocol, should also be recorded on the appropriate non-serious AE or SAE page of the CRF.

7. Measurement of Effect

7.1. Measurement of Anti-tumor Effect

MRI scan of Lesions

Response to contrast enhanced MRI will be assessed for measurable disease by the criteria outlined below. A baseline DCE-MRI will be performed before treatment begins. For the purposes of this study, patients will be evaluated approximately 1, 3, and 6 months (Days 30, 90, and 180) following the last TACE (after the operator determines that a lesion has been fully treated). Response will be assessed in two different ways: (1) the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and (2) European Association for the Study of the Liver (EASL) criteria for assessment of response to loco-regional therapy [2].

PET-CT scan of Lesions

Response to PET-CT will be assessed for measurable disease by the criteria outlined below. A baseline PET-CT will be performed before treatment begins. For the purposes of this study, patients will be evaluated approximately 12 weeks following the last TACE (after the operator determines that a lesion has been fully treated), then 12 weeks after that (**Days 90 and 180**). Response will be assessed in per lesion (see below).

CT scan of Lesions

Response to contrast enhanced CT will be assessed for measurable disease by the criteria outlined below. A CT will be performed before treatment begins. For the purposes of this study, patients will be evaluated approximately 4 weeks following the last TACE (after the operator determines that a lesion has been fully treated), then 8 weeks after that, and finally 12 weeks after that (Days 30, 90 and 180). Response will be assessed in per lesion (see below).

7.2. Guidelines for Evaluation of Measurable Disease

MRI Response Criteria: Evaluation of Lesions (RECIST Criteria)

- Complete Response – Complete disappearance of all target lesions.

- Partial Response – At least 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as a reference the baseline sum LD.
- Stable Disease – All other cases.
- Progressive Disease – At least a 20% increase in the sum of the LD of the target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

MRI Response Criteria: Evaluation of Lesions (EASL Criteria)

- Complete Response – Complete disappearance of all viable tumoral area and no new lesions. No new lesions may evolve during a 4 week period after initial documentation of response.
- Partial Response – Greater than 50% reduction in viable tumoral area of all measurable lesions via uptake of contrast.
- Stable Disease – All other cases.
- Progressive Disease – Greater than or equal to 25% increase in tumoral area of one or more measurable lesions or the appearance of new lesions.

8. Study Drug Information

8.1. Supply Drug Name

Lipiodol® **(**ethyl esters of iodized fatty acids of poppy seed oil)

Due to the current critical shortage of ETHIODOL®, Brand of Ethiodized Oil Injection, Guerbet is coordinating with the FDA to increase the availability of the ethyl esters of iodized fatty acids of poppy seed oil product. Guerbet has acquired the Ethiodol® NDA from Nycomed US Inc. effective May 7, 2010 and is working with the FDA to resume manufacturing of Ethiodol in the near future to ensure continued availability for the US patients. During this interim period, Guerbet, in conjunction with the FDA, is initiating a temporary importation of **LIPIODOL® ULTRA-FLUIDE**, ethyl esters of iodized fatty acids of poppy seed oil, to the United States market. **LIPIODOL® ULTRA-FLUIDE** contains the same drug components as **ETHIODOL®, Brand of Ethiodized Oil Injection**, (previously manufactured and marketed in the United States by Savage Laboratories, a subsidiary of Nycomed). **LIPIODOL® ULTRA-FLUIDE** is manufactured in compliance with European Good Manufacturing Practice (GMP) regulations by Delpharm Tours (France) for Guerbet.

At this time, no other entity except Guerbet is authorized by the FDA to import or distribute LIPIODOL® ULTRA-FLUIDE.

<u>Other names</u>

Ethiodol

<u>Classification</u>

Lipiodol is an X-ray contrast medium consisting of a preparation of ethyl esters of fatty acids, diiodized at C16 and C18. It is obtained from natural poppy seed oil which has undergone iodination and transesterification. The product is provided in the form of a solution for injection as a clear, pale yellow to amber solution packaged in 10 mL glass ampules. Lipiodol contains no excipients. Theiodine concentration of the preparation is 48 mg Iodine/mL.

<u>Mode of action</u>

Lipiodol is commonly used in arterial chemoembolization. Besides its opacifying properties, it acts as both an embolic agent and a carrier of chemotherapeutic agents to the tumor.

<u>Preparation</u>

In TACE procedures for liver tumor treatment, an emulsion is formed by mixing Lipiodol with the cytostatic drug.

Administration

In TACE procedures for HCC treatment, an emulsion is formed by mixing Lipiodol with the cytostatic drug and is injected intra-arterially through the hepatic artery to produce avascularity and infarction/necrosis of the tumor.

Availability

Due to the current critical shortage of ETHIODOL®, Brand of Ethiodized Oil Injection, Guerbet is coordinating with the FDA to increase the availability of the ethyl esters of iodized fatty acids of poppy seed oil product. Guerbet has acquired the Ethiodol® NDA from Nycomed US Inc. effective May 7, 2010 and is working with the FDA to resume manufacturing of Ethiodol in the near future to ensure continued availability for the US patients. During this interim period, Guerbet, in conjunction with the FDA, is initiating a temporary importation of **LIPIODOL® ULTRA-FLUIDE**, ethyl esters of iodized fatty acids of poppy seed oil, to the United States market. **LIPIODOL® ULTRA-FLUIDE** contains the same drug components as **ETHIODOL®, Brand of Ethiodized Oil Injection**, (previously manufactured and marketed in the United States by Savage Laboratories, a subsidiary of Nycomed). **LIPIODOL® ULTRA-FLUIDE** is manufactured in compliance with European Good Manufacturing Practice (GMP) regulations by Delpharm Tours (France) for Guerbet.

At this time, no other entity except Guerbet is authorized by the FDA to import or distribute LIPIODOL® ULTRA-FLUIDE.

9. Statistical Methods

9.1. Statistical Considerations

9.1.1. Analysis Sets

- Safety analysis set: all enrolled patients who completed at least 1 TACE procedure
- Full analysis set: all enrolled patients
- Per Protocol analysis set: all enrolled patients who complete the study and have no protocol deviations
- Modified Intent-to-Treat analysis set: all enrolled patients who complete all of their required pre-TACE, Day 0, and Day 1 procedures and evaluations, and complete at least 1 valid post-Day 1 imaging exam.

9.1.2. General Statistical Methods

- Type I error= 0.05 and will be 2-sided; 95% confidence intervals will be calculated.
- Summary statistics: For continuous measures, descriptive statistics will include the mean, standard deviation, min, median, max. For categorical measures, counts and proportions will be presented.
- missing values: No imputation for missing values will be performed.,
- There will be no adjustment for multiple comparisons in any of the planned analyses..
- Diagnostic analyses will be conducted to assess if non-parametric statistical methods should be used in lieu of the parametric methods.

Additional analyses may be performed, as appropriate, by YCAS statisticians.

9.2. Sample Size Justification

A sample size of 60 (HCC (n=30) and metastatic disease (n=30)) will allow for data collection and analysis to assess Lipiodol as an imaging biomarker in this pilot study. This sample size is based on feasibility and pilot study objectives.Operating characteristics were analyzed using PASS software (56) to estimate the effect size that can be detected with this sample size. A sample size of 60 achieves 80% power to detect a Pearson correlation coefficient of 0.35 with a two-sided significant level of 0.05. The sample size of 30 will allow for detecting a Pearson correlation coefficient of 0.49 in each subgroup. Similarly, for Spearman correlation, the minimum detectable correlations are 0.36 and 0.51 respectively, assuming a bivariate normal distribution.

Yale Center for Analytical Sciences (YCAS), which is the Biostatistics Shared Resources of Yale Cancer Center, will provide support to data analysis.

9.3. Analytic Plan

9.3.1. Analysis of the Primary Endpoint

- A single, representative, index lesion in each patient will be used to measure response.

- Percentage of lipiodol deposition (on the 24h non-contrast CT) will be scored as a continuous variable on a scale of 0-100, in addition to being categorized into 4 ordinal levels: ≤25%, >25-50%, >50-75%, >75%.

Percent lipiodol deposition in the tumor (obtained from 24h non-contrast CT, scored from 0-100) will be correlated with percent RECIST response, separately using contrast CT, MRI and PET imaging, and reported separately for each time point. The Pearson product-moment correlation will be used to measure the strength of the association, and 95% confidence intervals will be calculated.

Exact percent of lipiodol deposition (on the non-contrast CT, scored from 0-100) will be correlated with percent necrosis as reported on pathologic examination (if the patient goes on to hepatic surgical resection or transplantation; the percent necrosis of the lesion on a scale of 0-100) using Pearson's product-moment correlation, and 95% confidence intervals will be calculated.

Percent lipiodol deposition in the tumor (obtained from 24h non-contrast CT, scored from 0-100) will be correlated with percent EASL response, separately using contrast CT, MRI and PET imaging, and reported separately for each time point. The Pearson's product-moment correlation will be used to measure the strength of the association, and 95% confidence intervals will be calculated.

- Exact percent of lipiodol deposition (on the non-contrast CT, scored from 0-100) will be correlated with apparent diffusion coefficient (ADC) [53, 54] and with volumetic response [54, 55]using Pearson's product-moment correlation. and 95% confidence intervals will be calculated.Two correlations will be measured
  - The percent tumor ADC (scored from 0-100) as demonstrated on contrast MRI will be correlated with percent lipiodol deposition.
  - The percent tumor volumetric response (scored from 0-100) as demonstrated on contrast MRI will be correlated with percent lipiodol deposition.

9.3.2 Analysis of Secondary Endpoint

6-month survival will be analyzed using the Kaplan-Meier method to compare the progression free survival across the 4 ordinal Lipiodol retention strata described above. . If the proportional hazards assumption applies, a Kaplan-Meier logrank statistic will be reported. Median survival, with respective 95% confidence intervals, will be estimated by Lipiodol retention stratum

9.4. Exploratory analyses

- A correlation matrix for the RECIST/EASL scores using each imaging modality and the lipiodol deposition will be presented to assess agreement among all measures.
    - If the correlations allow, analysis of a multivariate RECIST/EASL response, consisting of the responses from the 3 imaging modalities as a single multivariate outcome measure, will be modeled as a function of lipiodol deposition.

Mixed model repeated measures analysis may be conducted to evaluate associations between lipiodol deposition at day 1 and timely change of each RECIST response measured by other image methods. Variance-covariance structures may be assessed to characterize patterns of association over time.

10. Regulatory Considerations

10.1. Clinical Trial Monitoring

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). The Yale Cancer Center Data and Safety Monitroing Committee (DSMC) auditing schedule includes a 100% review of the first 2 subjects, with a subsequent review schedule to be determined after but will include submission of safety dat at a minimum of every 6 months. In addition, a detailed monitoring plan will be established with the Yale Center for Clinical Investigation to assure comprehensive protection of the rights and safety of all subjects and the quality and integrity of the data. During the review process, the principal investigator and research monitors will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator, the IRB or Yale Cancer Center DSMC have the authority to stop or suspend the study or require modifications.

Given the now established safety and validity of the current Lipiodol-TACE procedure in our prior work, and experience with the combined co-administration of Lipiodol and TACE, we do not view the proposed studies as high risk. Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, a plan for monitoring the data and reporting on the safety of the study has been detailed in above sections. Monitoring will be performed in coordination with YCCI.

10.2. Records to be Kept

10.2.1. Case Report Forms (CRFs)

As used in this protocol, the term case report form (CRF) refers to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. All CRFs must be signed by the investigator to verify that the data contained on the CRFs is accurate. Any

corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

Usually, source documents are the hospital's or the physician's subject medical chart. In these instances the data collected on the CRFs must match the data in the corresponding charts. A CRF, or part of the CRF, may also serve as a source document.

10.2.2. Record Retention

To enable inspections and/or audits from regulatory authorities and the trial Sponsor, the investigator agrees to keep records, including the identity of all participating subjects (i.e. information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the IRB's policies, FDA's regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the trial Sponsor's written permission before disposing of any records, even if retention requirements have been met.

11. Ethics

11.1. Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All IRB correspondence should be retained in the Investigator File.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study will be conducted in accordance with the protocol, the

International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

11.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before implementation.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

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13. Appendix: Lipiodol package insert

LIPIODOL ULTRA-FLUIDE (480 mg I/ml), solution for injection.

Composition
Ethyl esters of iodized fatty acids of poppy seed oil* qs ad for one ampoule
* Iodine content: 48 %, i.e. 480 mg per ml.
Solution for injection in 5 ml or 10 ml ampoules.

Pharmaco-therapeutic class
Contrast agent.

Guerbet
BP 57400
95943 ROISSY CdG Cedex - FRANCE

When to use this medicinal product (therapeutic indications)
This medicinal product is an iodinated contrast agent. It has been prescribed to you for a radiological examination which is to be performed for diagnostic purposes or during a surgical procedure.
It can also be used to prevent iodine deficiency disorders when iodization of salt or drinking water cannot be undertaken.

WARNINGS !

When not to use this medicinal product (contraindications)
In radiology
This product MUST NOT BE ADMINISTERED by general intra-arterial, intravenous or intrathecal injection (injection of the product via the same route as for lumbar puncture).

In the treatment of iodine deficiency

This medicinal product MUST NOT BE USED in the following situations:
- if you suffer from hyperthyroidism,
- if you have a large, multinodular goiter and are aged over 45 years, due to the high risk of hyperthyroidism,
- if you are breast-feeding,

Special warnings
In diagnostic or interventional radiology
You should inform the doctor who is to perform the injection if you have or have had any problems of an allergic nature:
- allergic reactions to iodinated products, particularly during previous radiological examinations with contrast agents,
- food or drug-related allergies,
- urticaria,
- eczema,
- asthma,
- hay fever.

- Or if you suffer from cardiac or respiratory insufficiency.
- Or if you have a liver (cirrhosis) or thyroid disorder.

In iodine deficiency
Do not associate with other methods of iodine supplementation (iodization of salt or drinking water) which could increase the risk of hyperthyroidism.
It is advisable to avoid using this medicinal product in persons over the age of 45 years.
IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

Precautions for use
A premature polymerisation reaction may exceptionally occur between Lipiodol Ultra-Fluide and certain glues or batches of glues. Prior to any use of new batches of Lipiodol Ultra-Fluide or glue, it is mandatory to verify in vitro the compatibility between the glue used and Lipiodol Ultra-Fluide.
IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

Interactions with other medicinal products and other forms of interaction
IN ORDER TO AVOID ANY INTERACTIONS BETWEEN DIFFERENT MEDICINAL PRODUCTS, YOU MUST ALWAYS INFORM YOUR DOCTOR OR PHARMACIST OF ANY OTHER TREATMENT YOU ARE TAKING especially any treatment for hypertension or diabetes.

Pregnancy - Lactation
In iodine deficiency
If you are pregnant, your doctor may prescribe you iodine supplementation.
Due to the risk of hypothyroidism in neonates, Lipiodol is contraindicated during breast-feeding.

IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

AS A GENERAL RULE, IF YOU ARE PREGNANT OR BREAST-FEEDING, YOU SHOULD ALWAYS ASK THE ADVICE OF YOUR DOCTOR OR PHARMACIST BEFORE TAKING ANY MEDICINAL PRODUCT.

HOW TO USE THIS MEDICINAL PRODUCT

Dosage
Dosage varies according to the indication and is determined by the doctor performing the injection.

Method and route of administration
This product must be administered using a glass syringe.

In diagnostic radiology
lymphography: intralymphatic injection only
Diagnosis of liver lesions: selective intra-arterial injection only

In interventional radiology
Embolization with surgical glues: selective intra-arterial injection only

In iodine deficiency
Intramuscular injection only

Duration of treatment
This medicinal product will be administered to you in a single dose.

UNDESIRABLE EFFECTS

AS WITH ALL ACTIVE PRODUCTS, THIS MEDICINAL PRODUCT MAY CAUSE SOME UNDESIRABLE EFFECTS OF VARIABLE INTENSITY IN CERTAIN PERSONS:
possible onset of allergic reactions.

In diagnostic radiology
You may experience transient fever during the first few hours following the examination.
You may experience gastrointestinal disorders (nausea, vomiting or diarrhoea)

In iodine deficiency
You may presents signs of hyperthyroidism (weight loss, accelerated heart rate, increased intestinal transit rate, anxiety, insomnia, etc.).

PLEASE REPORT ANY UNDESIRABLE EFFECT WHICH IS NOT MENTIONED IN THIS LEAFLET TO YOUR DOCTOR OR PHARMACIST.

STORAGE

Do not use the product after the expiry date indicated on the outer packaging.

Special precautions for storage
Store protected from light.

DATE LEAFLET LAST REVISED
03/11/2005.

212129

Guerbet