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Official Title	Safety and Efficacy of Lipiodol® Ultra Fluid in Association with Surgical Glues during Vascular Embolization
NCT Number	NCT02625389

Protocol No. LUF-44-001

Safety and Efficacy of Lipiodol® Ultra Fluid in Association with Surgical Glues during Vascular Embolization

A Phase IV study

Design

Phase IV, multicenter, open label, single arm, post-marketing study

EU Post-Authorisation Safety Study (PASS)

EU PAS register number: EUPAS15045

COORDINATING INVESTIGATOR

Not applicable

SPONSOR

GUERBET, B.P. 57400, 95943 Roissy CdG Cedex, FRANCE

CLINICAL PROJECT MANAGER

[redacted]

[redacted]

PHARMACOVIGILANCE

[redacted]

[redacted] **pharmacovigilance.headquarters@guerbet-group.com**

[redacted]

STUDY SYNOPSIS

Study Title: Safety and Efficacy of Lipiodol® Ultra Fluid in Association with Surgical Glues during Vascular Embolization, a phase IV study	
EU PAS register number: EUPAS15045	
Study product: Lipiodol® Ultra Fluid (480 mg I/ml), solution for injection	**Active Ingredient(s):** Ethyl esters of iodized fatty acids of poppy seed oil (Lipiodol® Ultra Fluid)
Planned start date (First Subject In): Q3 2016 **Planned end date (Last Subject Out):** Q4 2017	**Participating countries (Number of sites):** India (Approx. 10 sites)

Study Objectives

Primary objective:

To evaluate the per-procedure safety of Lipiodol® Ultra Fluid in association with surgical glues during vascular embolization in routine medical practice.

Secondary objectives:

- To evaluate the safety of Lipiodol® Ultra Fluid in association with surgical glues up to one month after the last vascular embolization procedure.
- To evaluate the efficacy of Lipiodol® Ultra Fluid in association with surgical glues in vascular embolization.

Study design and methodology

Phase IV, multicenter, open label, single arm, post-marketing study.

The study is designed to investigate the safety of Lipiodol® Ultra Fluid in association with surgical glues as used according to each site medical practice during vascular embolization procedures. Subjects will be enrolled with the main condition that a vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues is part of their palliative/therapeutic strategy for their disease. The study procedure consists in vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues. According to the patient need and health status a second vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues may be considered by the investigator within the next 30 days after the first one. In this case, this procedure will be considered as a second study procedure. The per-procedure(s) safety evaluation will be enabled by appropriate records of safety events during the time frame of the study procedure(s). Safety evaluation will be completed at 30 +/-3 days after the last study procedure. Efficacy evaluation will rely on the level of lesion(s) obliteration after the study procedure compared to the pre-procedural target level of obliteration. Exploratory descriptive statistical methods will be used to evaluate safety and efficacy.

Number of subjects / sample size

No specific hypothesis could be set up and no statistical test planned, therefore number of subjects for the study is based on the requirement of 125 subjects as specified by SEC radio-diagnostic on January 19th 2017.

Eligibility criteria

Inclusion criteria:

To be included in the study, subjects must meet all the following inclusion criteria:

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EU PAS register number: EUPAS15045	
Study product: Lipiodol® Ultra Fluid (480 mg I/ml), solution for injection	**Active Ingredient(s):** Ethyl esters of iodized fatty acids of poppy seed oil (Lipiodol® Ultra Fluid)

1. Female or male adult subject older than 18 years
2. Subject presenting with vascular lesions/anomalies whether malformative (arterial, venous, arteriovenous, fistula) or tumoral (benign: hemangioma; malignant, angiosarcoma) eligible for vascular embolization of single or multiple lesion(s), using selective transarterial catheterization and Lipiodol® Ultra Fluid in association with surgical glues as only embolization material, in the next stage of the therapeutic or palliative strategy
3. Subject not previously treated for this/those lesion(s) by vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues
4. Subject able and willing to participate to the study
5. Subject having read the information, having consented to audio-visual recording of informed consent process and having provided his/her consent to participate in writing by dating and signing the informed consent form or subject unable to consent in writing whose free and voluntary consent is confirmed in writing by a legal representative or impartial witness, prior to any study related procedure being conducted

Non-inclusion criteria:

Subjects presenting with one or more of the following non-inclusion criteria must not be included in the study.

1. Subject scheduled for vascular embolization using embolization materials and radiopaque material other than Lipiodol® Ultra Fluid in association with surgical glues (e.g. embolizing fluids such as alcohol or sclerosant agents; particles; implants such as coils or microcoils or balloons; powdered metals such as tantalum or tungsten), whether in combination or alone.
2. Subject with known contra-indications to vascular embolization (e.g. severe coagulation disorder, infectious syndrome, presence of portal thrombosis)
3. Subject whose lesion(s) to be embolized is/are acutely bleeding
4. Subject presenting with life-threatening emergency situation
5. Subject with known contra-indication(s) to the use or with known sensitivity to Lipiodol® Ultra Fluid, to its ingredients or to drugs from a similar pharmaceutical class
6. Subject currently treated with beta-blockers, metformin or subject who stopped beta-blockers, metformin less that 2 days prior to vascular embolization as described in Lipiodol® Ultra Fluid Summary of Product Characteristics
7. Subject previously treated with Interleukin II as described in Lipiodol® Ultra Fluid Summary of Product Characteristics
8. Subject currently treated with effective anticoagulant therapy
9. Pregnant or breast-feeding female subject
10. Subject having received any investigational medicinal product within 7 days prior to enrolment
11. Subject with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the subject's safety or her/his ability to participate to the study
12. Subject unlikely to comply with the protocol, e.g. uncooperative attitude, and unlikely to complete the study
13. Subject related to the Investigator or any other study staff or relative directly involved in the

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study conduct	

Investigational Medicinal Product(s) administration

The product investigated is Lipiodol® Ultra Fluid used in association with surgical glues, together referred to as "mixture". The glue should be chosen according to the investigator and site practice and knowledge. The mixture should be administered via selective arterial catheterization only.

The dose of Lipiodol® Ultra Fluid administered during the embolization procedure depends on lesion size. The Lipiodol® Ultra Fluid and the surgical glue mixture may vary from 20 to 80% but usually consists of a 50/50 mixture.

The volume of Lipiodol® Ultra Fluid injected should not exceed 15 ml during the procedure of vascular embolization.

Study duration

The study consists in subject enrolment visit and then a first procedure of vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues (study procedure) that may occur on the same day or within 7 days. A second optional vascular embolization procedure will be considered in the study if done within 30 days after the first one. Safety follow-up within 30 +/- 3 days after the last study procedure will complete the subject participation. The maximum study duration for a subject is 70 days. The minimum participation for a subject who undergoes one study procedure is 28 days.

Evaluation criteria

Primary criterion:

Number and percentage of subjects experiencing Adverse Drugs Reactions (ADRs) after each administration of Lipiodol® Ultra Fluid in association with surgical glues until leaving the catheterization laboratory

Secondary criteria:

- ADRs occurring from the first administration of mixture until the end of follow-up
- Adverse events (AEs)
- Target obliteration and post-procedure obliteration per lesion will be evaluated respectively before the first procedure and after each procedure according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate.
- Successful lesions embolization expressed as the lesions achieving the targeted percentage of obliteration

Procedure for Reporting Serious Adverse Events

SAEs occurring from written informed consent until completion of the study for each subject are to be reported by the investigator to Guerbet Pharmacovigilance department (by Fax #: + 33 (0)1 45 91 67 70 or by e-mail to: pharmacovigilance.headquarters@guerbet-group.com), IRB/IEC ((Institutional Review Board/ Independent Ethics Committee) and Licensing Authority (DCGI) immediately and within 24 hours of occurrence of event, using a duly completed SAE report form provided by Guerbet

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with study documents, even if it is obvious that more data will be needed in order to draw any conclusion.

The Investigator and Guerbet shall forward their reports after due analysis, to the Chairman of the Ethics Committee, Licensing Authority (DCGI office) and Head of Institution where the trial has been conducted within 14 calendar days of occurrence of the serious adverse event.

Statistical methods

Descriptive statistical methods will be used to report all safety and efficacy assessments.

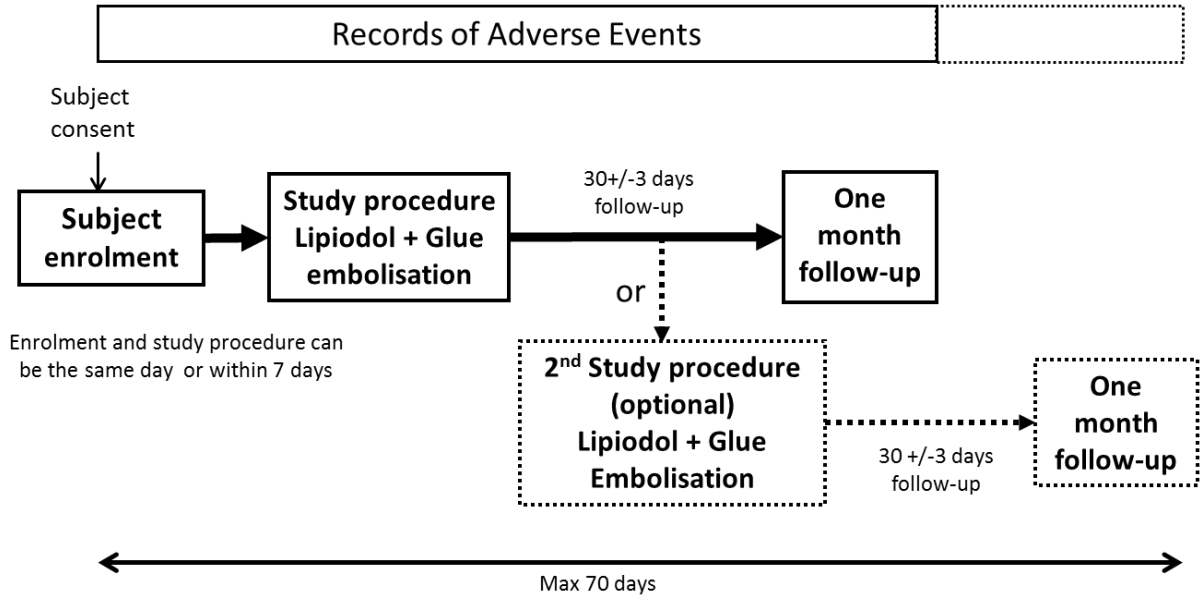
For assessment of the safety, occurrence of ADRs and AEs will be tabulated in terms of number and percentage as well as their associated characteristics such as intensity, actions taken, outcome, causal relationship to the mixture of Lipiodol® Ultra Fluid associated with surgical glues and causal relationship to the study procedure of vascular embolization.

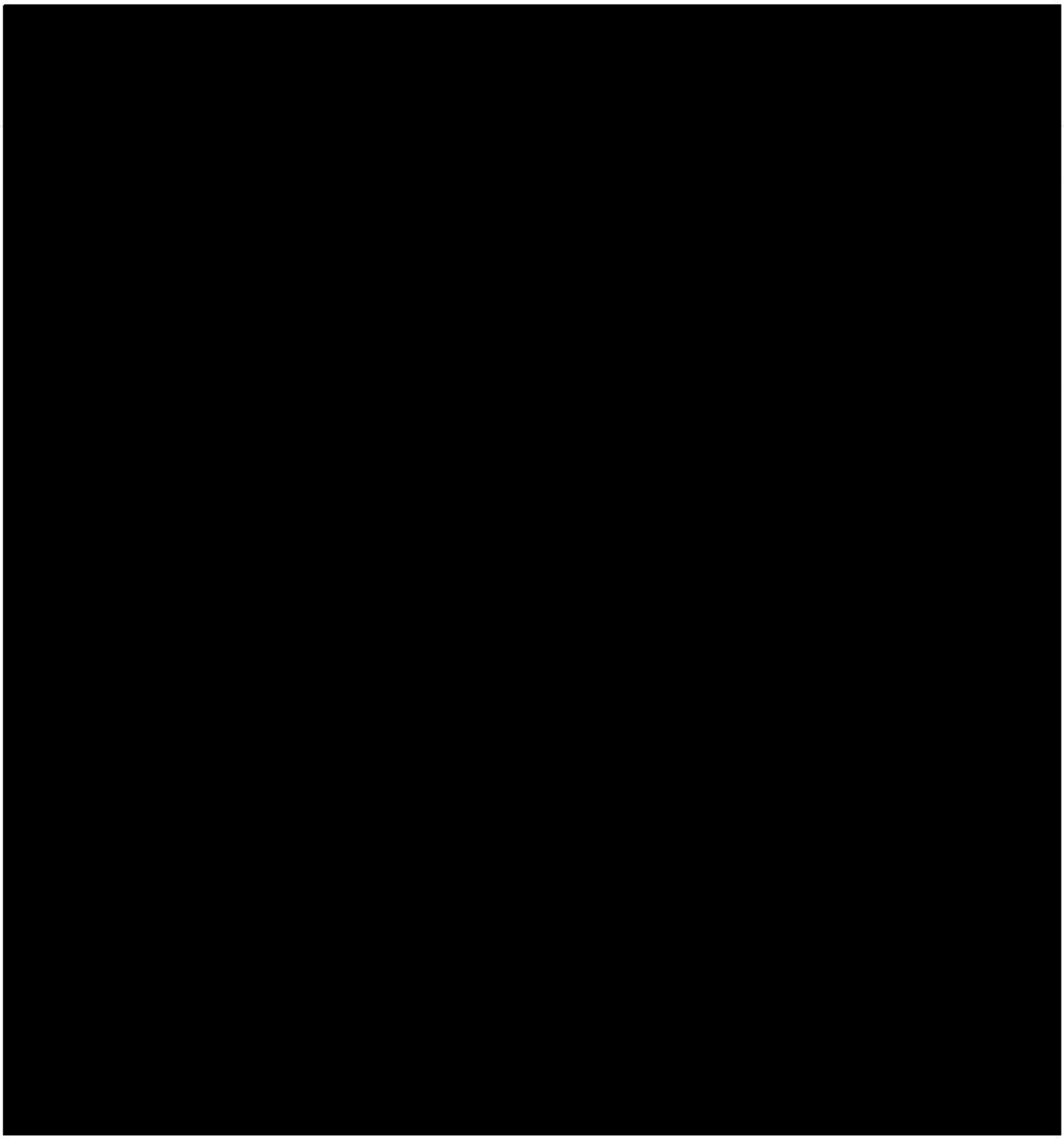
The efficacy of the procedure will be described in terms of number and frequency of obliteration (target and post-procedure) scores and in terms of number and frequency of lesions embolizations matching target.

STUDY FLOW CHART

	Enrolment	First study procedure *Consecutively or within 7 days after enrolment*	Optional Second study procedure *Only if within 30 days after first study procedure*	1 month Follow-up *30+/-3days after the last study procedure*
Written informed consent and audio-video record	X			
Eligibility criteria	X			
Demographic data and medical history	X			
Therapeutic / palliative strategy per lesion to be treated	X			
Reason for having a second study procedure			X	
Target lesion(s) obliteration prior to the procedure	X		X	
Conditions of use of Lipiodol® Ultra Fluid in association with surgical glue for vascular embolization		X	X	
Post-procedure efficacy evaluation of lesion(s) obliteration		X	X	
Records of any other therapeutic/palliative procedure				X
Concomitant treatments	⟷			
Adverse event(s)	⟷			

STUDY DIAGRAM





ABBREVIATIONS

ADR	Adverse Drugs Reaction
AE	Adverse Event
AIS	All Included Set
CTA	Computerized Tomography-Angiography
CRF	Case Report Form
CDSCO	Central Drugs Standard Control Organization
DCGI	Drugs Controller General of India
DSA	Digital Subtraction Angiography
eCRF	Electronic CRF
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
I	Iodine
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic Resonance Angiography
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SSF	Study Site File
US	Ultrasound
WHO	World Health Organization

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1 INTRODUCTION AND STUDY RATIONALE

Lipiodol® Ultra Fluid was first developed in 1901 and became the first iodinated contrast agent for Radiology in 1926. It is registered in the World Health Organization (WHO) list of essential drugs.

Lipiodol® Ultra Fluid has been recently approved by the Drugs Controller General of India (DCG(I)) for indications in diagnostic Radiology : lymphography, diagnosis of liver lesions; in interventional Radiology: vascular embolization with surgical glues; and in endocrinology: prevention of iodine deficiency disorders.

The DCG(I) required Guerbet to conduct a phase IV study with at least 100 subjects as a condition to the approval of Lipiodol® Ultra Fluid. The present study was planned to fulfill this requirement.

In this study, Lipiodol® Ultra Fluid will be administered in association with surgical glue to adult subjects eligible for transarterial vascular embolization as according to each site practice and according to its applicable Summary of Product Characteristics (SmPC).

Vascular embolization also known as embolotherapy consists in a procedure of percutaneous selective catheterization during which embolization material is placed in the vascular bed of a lesion with aim to obtain partial or complete vascular obliteration. This procedure may be used as first-line stand-alone therapeutic or palliative strategy or as one of the procedures of a multi-staged strategy involving other procedures such as surgery or radiosurgery [1; 2]. Vascular embolization is commonly used in a wide range of lesions types (e.g. vascular malformations, neoplasms, hemorrhagic lesions) with diverse anatomical locations and functional consequences.

A variety of embolization materials are used during procedures of vascular embolization either alone or in combination, including fluid agents (e.g. surgical glues, alcohol, sclerosant agents, sponges), particulate agents (e.g. gelatin, microspheres) and implants (e.g. microcoils, balloons). These embolization agents have different properties and all lead to vascular obliteration. Surgical glues (most frequently cyanoacrylate derivates) are synthetic liquids which properties of adhesion to tissues and rapid polymerisation create a non-resorbable endovascular mass [3].

The decision to proceed with a procedure of vascular embolization and the choice of embolization material(s) depends greatly on the patient's clinical presentation, the vascular architecture and size of the lesion(s) and the clinical objectives (reduction of hemorrhagic risk, blood flow redistribution, palliative treatment of unresectable malignant tissues etc.).

Lipiodol® Ultra Fluid is an iodinated oily contrast which has been used for arterial chemoembolization of hepatic tumors since the early eighties [4; 5]. It has since been used in combination with surgical glues at various ratios for endovascular embolization of vascular anomalies such as aneurysms, fistulas or vascular neoplasms [6; 7; 8].

The usefulness of Lipiodol® Ultra Fluid added to surgical glues in this indication is four fold: (i) it increases the polymerisation time hence limiting risks of clogging of the catheters (ii) it permits to adjust the viscosity of the embolic mixture to the lesion angioarchitecture and to the blood flow; (iii) it possesses a transient plastic embolic ability by slowing arterial circulation and adjusting to the size of small nidus vessels [9]; (iv) it allows the fluoroscopic visualization of the embolic mixture due to iodine radiopacity.

The present study aims at depicting the safety of Lipiodol® Ultra Fluid in association with surgical glues in the routine medical practice of transarterial vascular embolization using this association of products as embolization agents. Subjects with a large range of clinical conditions and target lesions are expected to be included.

2 STUDY OBJECTIVES

The objectives of this phase IV study are to evaluate the safety and efficacy of Lipiodol® Ultra Fluid in association with surgical glues used for vascular embolization.

2.1 Primary Objective

To evaluate the per-procedure safety of Lipiodol® Ultra Fluid in association with surgical glues during vascular embolization.

2.2 Secondary Objectives

- To evaluate the safety of Lipiodol® Ultra Fluid in association with surgical glues up to one month after the vascular embolization procedure.
- To evaluate the efficacy of Lipiodol® Ultra Fluid in association with surgical glues in vascular embolization.

3 STUDY DESIGN

3.1 Protocol Description

This study is a phase IV, multicenter (8 to 10 sites in India), open label, single arm, post-marketing study.

The study is designed to investigate the safety of Lipiodol® Ultra Fluid in association with surgical glues used according to each site medical practice of vascular embolization. Subjects will be enrolled with the main condition that a procedure of vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues is part of their therapeutic/palliative strategy for their disease. The vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue will be administered as study procedure. According to the patient need and health status a second vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue may be considered by the investigator within the next 30 days after the first one. In this case, this procedure will be considered as a second study procedure. The per-procedure safety evaluation will be enabled by appropriate records of safety events during the time frame of the procedure of vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues. Safety evaluation will be completed with safety records within 30 +/-3 days after the embolization procedure. Efficacy evaluation will rely on the level of lesion(s) obliteration after embolization compared to the pre-procedural target level of obliteration. Exploratory descriptive statistical methods will be used to evaluate safety and efficacy, using both the total population and subsets of subjects with similar clinical conditions.

Sites selection

The selection of participating sites will be conducted by Guerbet or its delegate. Participating sites must have appropriate medical equipment, devices and products. Staff must be trained, qualified and routine practitioners of the procedures of vascular embolization and routine users of the medical equipment, devices and products involved in this study. According to DCGI requirements, Guerbet will make all efforts to select 50 % sites from government institutes and sites from different geographical parts of India.

Guerbet or its delegate will be responsible for collecting documentation, such as CV, to ensure that the sites have the competence to perform the study.

3.2 Study Duration

The study consists in subject enrolment and the vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue (study procedure) that may occur on the same day or within the next 7 days. Any second optional vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue maximum within the next 30 days after the first one will be considered as second study procedure. A safety follow-up at the next 30+/-3 days after the last study procedure will complete the subject participation. The maximum study duration for a subject is 70 days.

3.3 Interim analysis

Not applicable.

3.4 Study Committee(s)

A data safety monitoring board (DSMB) will be set up within Guerbet including a safety physician, Guerbet medical expert and the clinical project manager. This DSMB will review the following monitored data on a quarterly basis as a minimum:

- AEs and SAEs,
- Fatal SAE as soon as it is reported,
- Any reason (adverse event or completion of the treatment/palliative strategy) of any new therapeutic / palliative procedure administration within the follow-up period.

4 SUBJECT SELECTION

4.1 Inclusion Criteria

To be included in the study, the subject must meet all the following inclusion criteria:

1. Female or male adult subject older than 18 years
2. Subject presenting with vascular lesions/anomalies whether malformative (arterial, venous, arteriovenous, fistula) or tumoral (benign: hemoangioma; malignant, angiosarcoma) eligible for vascular embolization of single or multiple lesion(s), using selective transarterial catheterization and Lipiodol® Ultra Fluid in association with surgical glues as only embolization material, in the next stage of the therapeutic or palliative strategy
3. Subject not previously treated for this/those lesion(s) by vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues
4. Subject able and willing to participate to the study
5. Subject having read the information, having consented to audio-visual recording of informed consent process and having provided his/her consent to participate in writing by dating and signing the informed consent form or subject unable to consent in writing whose free and voluntary consent is confirmed in writing by a legal representative or impartial witness, prior to any study related procedure being conducted (as described in section 13.3)

4.2 Non Inclusion Criteria

Subjects presenting with one or more of the following non-inclusion criteria must not be included in the study:

1. Subject scheduled for vascular embolization using embolization materials and radiopaque material other than Lipiodol® Ultra Fluid in association with surgical glues (e.g. embolizing fluids such as alcohol or sclerosant agents; particles; implants such as coils or microcoils or balloons; powdered metals such as tantalum or tungsten), whether in combination or alone
2. Subject with known contra-indications to vascular embolization (e.g. severe coagulation disorder, infectious syndrome)
3. Subject for whom lesion(s) to be embolized is/are acutely bleeding
4. Subject presenting life-threatening emergency situation
5. Subject with known contra-indication(s) to the use or with known sensitivity to Lipiodol® Ultra Fluid, to its ingredients or to drugs from a similar pharmaceutical class
6. Subject currently treated with beta-blockers, metformin or subject who stopped beta-blockers, metformin less that 2 days prior to vascular embolization as described in Lipiodol® Ultra Fluid Summary of Product Characteristics
7. Subject previously treated with Interleukin II as described in Lipiodol® Ultra Fluid Summary of Product Characteristics
8. Subject currently treated with effective anticoagulant therapy
9. Pregnant or breast-feeding female subject
10. Subject having received any investigational medicinal product within 7 days prior to enrolment

11. Subject with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the subject's safety or her/his ability to participate to the study
12. Subject unlikely to comply with the protocol, e.g. uncooperative attitude, and unlikely to complete the study
13. Subject related to the Investigator or any other study staff or relative directly involved in the study conduct

4.3 Subject Identification

After having obtained the written informed consent and verified that all eligibility criteria are met, subjects will be included in the study and will be allocated a unique identification number consisting in 6 digits: 2 digits for country identification, 2 digits for site identification and 2 digits (allocated sequentially) for subject identification.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

The product investigated is Lipiodol® Ultra Fluid used in association with surgical glues, together referred to as "mixture".

Lipiodol® Ultra Fluid will be manufactured, labeled, packaged and released in accordance with local applicable requirement.

5.1 Lipiodol® Ultra Fluid

Lipiodol® Ultra Fluid (480 mg I/ml) is a 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.

Refer to applicable SmPC.

5.2 Packaging, Labeling, Storage

The IMP will consist of one 10 ml type I glass ampoule of Lipiodol® Ultra Fluid packaged in a carton box and labeled as per Indian requirements. It shall be stored according to its applicable SmPC, i.e. protected from light.

Each IMP will be identified with a single ID of 4 digits and labeled with a single use detachable label that will allow ensuring accuracy of IMP allocation per subject.

In case of a second vascular embolization procedure for a single subject, a second IMP will be allocated to the subject.

The participating sites must ensure that ampoules are securely stored in order to avoid misuse.

5.3 Condition of Investigational Medicinal Product Administration

Lipiodol® Ultra Fluid will be administered in association with surgical glues.

Commercially available surgical glues will be used by the sites according to the investigator choice and usual practice. Brand name of the surgical glues used and applicable SmPCs will be collected.

Vascular embolization with liquid agents is a complex and delicate technique which should only be performed by trained physicians in an appropriate medicosurgical setting.

A premature polymerisation reaction may exceptionally occur between Lipiodol Ultra Fluid and certain glues or batches of glues. Prior to any use of new batches of Lipiodol® Ultra Fluid or glue, it is mandatory that investigators verify *in vitro* and document the compatibility between the glue used and Lipiodol Ultra-Fluid.

The dose of Lipiodol® Ultra Fluid administered during the embolization procedure depends on lesion size. The Lipiodol® Ultra Fluid and liquid embolizing agent (surgical glue) mixture may vary from 20 to 80% but usually consists of a 50/50 mixture.

The Lipiodol® and surgical glue mixture should be administered via **selective arterial catheterization only**.

The volume of Lipiodol® Ultra Fluid injected should not exceed 15 ml during each procedure of vascular embolization.

5.4 Investigational Medicinal Product Compliance and Accountability

The investigator, the hospital pharmacist, or other allowed personnel will keep accurate records of Investigational Medicinal Products accountability at site level as well as accurate records of the batch numbers and IMP(s) given to each subject.

The dosing information will be recorded in individual subject's records. When protocol required IMP administration conditions are not followed, reason(s) will be given and recorded by the investigator.

6 CONCOMITANT TREATMENTS

6.1 General considerations

Any medication present from 7 days before first vascular embolization or concomitant medication administered during the study will be recorded in the subject Case Report Form (CRF). The following information will be captured:

- Drug (brand name or generic name)
- Route of administration
- Indication
- Purpose (medical history/AE/pre-medication/other)
- Duration of treatment (start and stop period from enrolment and from the IMP administration)

Any contrast media administered during the reporting period should be included.

Anesthetic medication administered for other procedures than the study procedures should not be reported.

6.2 Interaction with other medications or contraindications

Interleukin II:

The risk of developing a reaction to the contrast agents is increased in the event of previous treatment with interleukin II (IV route): skin rash or, more rarely, hypotension, oliguria, or even renal failure. Please refer to non-inclusion criteria N°7.

Anticoagulants:

Interventional radiology and catheter angiogram may be risky in patients taking anticoagulants. Their stop should be evaluated before to decide to enroll the patient. Please refer to non-inclusion criteria N°8.

Diuretics:

In the event of dehydration provoked by diuretics, the risk of acute renal failure is increased, especially when high doses of iodinated contrast agents are used. Precautions for use: re-hydration before administration of the iodinated contrast agent.

For the following medications, their stop within two days before embolization procedure should be evaluated before to decide to enroll the patient. Please refer to non-inclusion criteria N° 6:

Beta-blockers:

In the event of shock or hypotension due to iodinated contrast agents, beta-blockers reduce the effectiveness of the cardiovascular mechanisms that compensate for blood-pressure disturbances.

Treatment with beta-blockers should be stopped, whenever possible, before the vascular embolization procedure.

Metformin:

In diabetic patients, intra-arterial administration of Lipiodol® Ultra Fluid may cause lactic acidosis induced by diminished renal function.

Treatment with metformin must be suspended 48 hours before the investigation and only restarted 2 days after the vascular embolization procedure.

7 EVALUATION CRITERIA

7.1 Primary Criterion

The primary evaluation criterion is the number and percentage of subjects experiencing adverse drugs reactions (ADRs) occurring during the course of each vascular embolization procedure after administration of Lipiodol® Ultra Fluid in association with surgical glues and before catheterization laboratory discharge.

Adverse events (AEs) will be collected during subject participation to the study, i.e. from written informed consent until end of the follow-up period. Site investigators will be required to assess the causal relationship to the mixture of Lipiodol® Ultra Fluid associated with surgical glues as described in section 10.1.3. All AEs assessed as related to the mixture of Lipiodol® Ultra Fluid and surgical glues will be qualified as ADRs.

7.2 Secondary Criteria

The study will evaluate additional safety criteria:

- ADRs from the first administration of Lipiodol® Ultra Fluid in association with surgical glues up to the end of the follow-up period.
- The complete set of AEs collected during the study, regardless of causal relationship assessments, from written informed consent until end of the follow-up period.

Efficacy will be explored with the following assessments:

- Target obliteration per lesion evaluated before the first procedure according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate
- Post-procedure obliteration per lesion will be evaluated after each procedure according to the same 4 level-obliteration-score
- Successful lesions embolization, expressed as the lesions achieving the targeted percentage of obliteration

  At subject enrolment visit, all lesions designated for vascular embolization using Lipiodol® Ultra Fluid associated with surgical glue will be described on the basis of the most recent angiogram and will be associated to a target percent obliteration (i.e. at least x% obliteration or approximately x% obliteration) that is expected to be reached during the procedure. After the procedure, the percent obliteration will be assessed on earliest available angiogram (e.g. Digital Subtraction Angiography (DSA), Computerized Tomography-Angiography (CTA), Magnetic Resonance Angiography (MRA), vascular imaging Ultrasound (US), Doppler US) consistence with the target obliteration will be provided by the investigator.

8 NUMBER OF SUBJECTS

According to Guerbet best update knowledge of the use of Lipiodol® Ultra Fluid along with glues in embolization procedure no particular safety signal with a related incidence could lead to design a safety study with a specific sample size. No specific hypothesis could be set up and no statistical test planned, therefore number of subjects for the study is based on the requirement of 125 subjects as specified by SEC radio-diagnostic on January 19th 2017. Subjects' data will be analyzed with descriptive statistics investigating in clinical routine the general safety and efficacy of the procedure in an exploratory fashion.

9 STUDY SCHEDULE AND PROCEDURES

The study consists in the following procedures:

- Subject enrolment,
- First study procedure (vascular embolization procedure using the mixture Lipiodol® Ultra Fluid associated with surgical glue) that may occur on the same day or within 7 days after the subject enrolment,
- An optional second study procedure if done within 30 days after the first one,
- A safety follow-up within 30 +/-3 days after the last procedure using Lipiodol® Ultra Fluid associated with surgical glues that could be a visit, a phone call or completed with available medical records.

9.1 Enrolment Visit

After the site staff has checked the eligibility criteria, the informed consent will be retrieved as described in section 13.3 and the following information will be collected:

- Demographic data: age, sex, height, weight
- Inclusion and non-inclusion criteria verification
- Medical history: past and current diseases (if relevant for the study) including allergies
- Indication for the vascular embolization procedure: number of lesions to be treated, lesion type and location
- Therapeutic/palliative strategy for the lesions to be treated: previous procedure, and if a second vascular embolization procedure using Lipiodol® Ultra Fluid in association with surgical glues is scheduled within the next 30 days after the first one, the next procedure scheduled after study procedure(s), target percent obliteration for the first study procedure (evaluated according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate)
- Safety information: adverse event(s) whether serious or not. For more information on safety reporting, refer to Section 10
- Concomitant medications

9.2 First Study procedure

The study procedure is a vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue (the mixture) via selective arterial catheterization.

Site staff will collect the following information related to the first study procedure:

- The conditions of mixture administration: date of the procedure, time of first injection of the mixture, associated surgical glue (brand name), puncture site, time leaving the catheterization laboratory, number of injections, and per injection : concerned lesion, ID number of IMP, mixture ratio of Lipiodol® Ultra Fluid to surgical glue, total volume, catheter flush if any (yes/no)
- Changes in therapeutic/palliative strategy introducing additional embolization material
- Post-procedure obliteration (evaluated according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate) per lesion assessed on

earliest available angiogram after the first embolization procedure (e.g. DSA, CTA, MRA, US, Doppler US)

- Safety information: adverse event(s), whether serious or not. For more information on safety reporting, refer to Section 10
- Concomitant medications

9.3 Second study procedure (optional)

According to the patient need and health status, a second vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue may be considered by the investigator within the next 30 days after the first one.

In this case, this procedure will be considered as a second study procedure and the following will be recorded:

- Date and reason (adverse event, completion of study disease therapeutic/palliative strategy)
- Concerned lesions to be treated including new lesions, and target percent obliteration for the second procedure
- The condition of mixture administration: time of first injection of the mixture, associated surgical glue (brand name), puncture site, time leaving the catheterization laboratory, number of injections, and per injection : concerned lesion, ID number of IMP, mixture ratio of Lipiodol® Ultra Fluid to surgical glue, total volume, catheter flush if any (yes/no)
- Changes in therapeutic/palliative strategy introducing additional embolization material
- Post-procedure obliteration (evaluated according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate) per lesion assessed on earliest available angiogram after the second study procedure (e.g. DSA, CTA, MRA, US, Doppler US)
- Safety information: adverse event(s), whether serious or not. For more information on safety reporting, refer to Section 10
- Concomitant medications

9.4 Safety follow-up at one month

Collection of data relevant to the safety follow-up of the subject is expected at 30 +/- 3 days after the last procedure using Lipiodol® Ultra Fluid associated with surgical glues

Safety follow-up is expected when at least one administration of the mixture Lipidiol® Ultra Fluid in association with surgical glues will occur.

The following information will be collected by the site:

- Date and kind of follow-up (visit, phone, medical records)
- New therapeutic/palliative procedure if any within the period, administered to the subject for the study disease: Date, type (embolization using other material, surgery, radiosurgery, other) and reason (adverse event, completion of study disease therapeutic/palliative strategy).
- Safety information: adverse event(s), whether serious or not. For more information on safety reporting, refer to Section 10
- Concomitant medications

10 SAFETY REPORTING

10.1 Adverse Event

10.1.1 Definition of Adverse Event

An Adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related.

10.1.2 Recording/Collection of Adverse Events

The Investigator or his/her designee will invite the subject to report any abnormality experienced as part of the usual clinical follow-up.

All AE, whether considered as related or not to the administration of the mixture of Lipiodol® Ultra Fluid and surgical glues and/or the study procedure of vascular embolization should be reported in the medical file and the CRF and followed up from onset to resolution or stabilization of sequelae. If no follow-up is performed, the investigator must provide a justification.

In order to ensure complete safety data collection, all AEs occurring during the time of the subject's participation in the study, must be reported and followed. As reminder the subject's participation is defined as the period from written informed consent to the last study observation and defined in Section 11.

The following safety information must be collected by the investigator using the same procedure as AEs: medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, suspicion of transmission of an infectious agent via the product, reactions resulting from an occupational exposure, unusual failure in efficacy, overdose (symptomatic or not), all reports of pregnant or breastfeeding women exposure even if uneventful, all reports of suspected drug-drug interaction with another product (symptomatic or not).

In the context of the study, overdose is defined as a total volume of Lipiodol® Ultra Fluid administered of 15mL during a procedure of vascular embolization using Lipiodol® Ultra Fluid in association with surgical glues.

10.1.3 Description of Adverse Events

The following guidelines and definitions should be used by the investigator for the description of an AE when reporting information:

- **Nature of AE:** preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The investigator must report AE using standard medical terminology. The same terms should be used in the source documentation and in the CRF.
- **Date and time of onset:** date and clock time of the AE start
- **Intensity:**
    - Mild: the subject is aware of the sign or symptom, but it does not interfere with her/his usual daily activities and/or it is of no clinical consequence

- Moderate: the AE interferes with the usual daily activities of the subject or it is of some clinical consequence
- Severe: the subject is unable to work normally or to carry out his/her usual daily activities, and/or AE is of definite clinical consequence.

- **Date of the event end** (or consolidation): The real date of event end will be entered if the event has come to its end before the date of end of subject's follow-up. If the AE is still ongoing by the time of end of study follow-up for the subject, the subject should be followed-up until AE resolution or a justification should be provided by the Investigator (e.g. chronic disease or subject lost to follow-up) in the medical file.
- **Causal relationship to the mixture of Lipiodol® Ultra Fluid and surgical glue :**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the mixture. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no mixture has been administered (pre-administration period) or when no causal relationship exists between the mixture and the event, but an obvious alternative cause exists (e.g. the subject's underlying medical condition or concomitant therapy).

  All AEs assessed as related to the mixture will qualify as ADRs in the evaluation of primary and secondary criteria, as described in section 7.
- **Causal relationship to the study procedure of vascular embolization :**
  - Related
  - Not related
- **Outcome:**
  - Recovered/Resolved: the AE is no longer present at any intensity.
  - Recovered/Resolved with sequelae: the AE is resolved but residual effects are still present.
  - Not recovered/Not Resolved: the AE is still present at the last contact with the subject.
  - Fatal: this AE caused or directly contributed to subject's death.
- **Action taken with regard to administration of the mixture:**
  - No action: for AE occurring during the pre-treatment/procedure or post-treatment/procedure period, or if the mixture dosing/administration remained the same in spite of AE being present.
  - Study products withdrawn: the mixture was not administered or was stopped.
- **Other action taken:**
  - AE-targeted medication: the subject took a medication (either prescription or non-prescription) specifically for this AE. The medication(s) should be reported in the appropriate section of the CRF ("concomitant drug" section)
  - Other AE-targeted action: subject used other therapeutic measures (e.g. ice, heating pad, brace, cast…) or subject underwent a procedure (physiotherapy, additional laboratory test…) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the CRF ("Action other than drug administered for the AE" section)
- **Assessment of the seriousness of the AE**: see Section 10.2 for serious adverse event (SAE) definition.

10.2 Serious Adverse Event

10.2.1 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing in subject's hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important: adverse events that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. In case of a SAE, the investigator is responsible for the measures to be taken to ensure the safety of the study participants.

The following safety issues qualify for immediate reporting to Guerbet since they may alter the current benefit-risk assessment of the mixture, or would be sufficient to consider changes in the mixture administration or in the overall conduct of the study:

- Any serious and/or unexpected adverse event that occurs after the subject has completed the study and that is considered as related to the mixture by the investigator (causality not excluded).
- Any new event likely to affect the safety of the subjects and that may be related to the conduct of the study such as:
    - A SAE which could be associated with the study and which could modify the conduct of the study;
    - A significant hazard such as an unusual failure in efficacy;

Any suspicion of transmission of an infectious agent via the mixture should be considered as a serious and processed as an SAE.

In addition, any adverse reaction resulting from an occupational exposure may be directly reported to Guerbet.

Severe / Serious: the term "severe" is often used to describe the intensity (severity) of a specific event (within the scale mild, moderate, severe). The event itself, however, may be of relatively minor medical significance. This is not the same as "serious", which is based on subject/event outcome or action criteria.

In this protocol, the following situations will not be considered as SAE, providing that they are clearly documented as such in the subject's source data:

- Any hospitalization that had been planned before the study and that will take place during the study, and provided with no aggravation of the disease to which it is related.

- Therapeutic /palliative procedure administration for the study disease (vascular embolization, surgery, radiosurgery etc.) scheduled or not at the time of enrolment, with or without of Lipiodol® Ultra Fluid associated with glues, and provided with no aggravation of the disease to which it is related. Reasons for all those reported procedures will be reviewed by the DSMB in order to ensure of no safety concern and under-reporting.
- Hospitalizations, which are not associated to an AE (such as hospitalization for check up).

10.2.2 Procedure for Reporting Serious Adverse Events

SAEs occurring from written informed consent until completion of the study for each subject are to be reported by the investigator to Guerbet Pharmacovigilance department, IRB/IEC ((Institutional Review Board/ Independent Ethics Committee) and Licensing Authority (DCGI). **immediately and within 24 hours** of occurrence of event, using a duly completed SAE report form provided by Guerbet with study documents, even if it is obvious that more data will be needed in order to draw any conclusion.

Guerbet Pharmacovigilance department

- **By Fax #: + 33 (0)1 45 91 67 70**
- **Or by e-mail to: pharmacovigilance.headquarters@guerbet-group.com**

In case of emergency, Guerbet Pharmacovigilance department may be contacted at:**+33 (0)145915000.**

The initial and follow up reports shall identify the study subject by his/her Identification Number assigned for the purpose of the study.

In order to allow the assessment and eventual subsequent regulatory reporting of the case, the following minimum information should be filled in:

- Subject's details including subjects initials, age (or date of birth), gender, weight , height and subject's study enrolment number,
- Description of event by reporting a diagnosis or if not available, symptoms,
- Name of the IMP (generic name) and the name of the surgical glue
- Investigator reporting details

Additional information and/or documentation (e.g. autopsy, outcome, lab reports…) will be required by Guerbet in a timely fashion to ensure accurate follow-up and assessment of each case. This information/documentation should be forwarded, anonymized, with a new SAE report form specifying basic information (follow-up report number, patient details and number, adverse event, IMP, causal relationship) and the new information detailed below (but not limited to):

- Indication(s) for which the mixture was prescribed or tested
- Date and time of onset of the event and of knowledge by study physician
- IMP dosage form, date and time of administration, dose and volume administered, mixture ratio with surgical glue and volume of surgical glue, route of administration,
- End date and time of the event (will be reported in a follow-up report if the event is still ongoing at the time of first notification)
- Subject's medical history relevant to the assessment of the event
- Other treatments: names, indications, dosages, routes of administration, start and end dates and times.
- Expectedness of SAE (expected / unexpected)
- De-challenge and re-challenge when applicable
- Action taken towards the mixture.
- Setting (e.g. hospital/home/nursing home/out patient clinic

- Causal relationship to the mixture
- Causal relationship to the study procedure
- Outcome at the time of reporting
- Treatments
- Date of reporting the event to Licensing Authority and to Ethics Committee overseeing the site

Any event leading to a SAE report should be reported in the medical file and in the AE section of the Case Report Form as requested in Section 10.1.2.

SAEs should be followed up by the investigators until complete recovery of the subject or, if not possible, until stabilization of sequelae. The investigator may be requested by Guerbet to provide follow-up information in order to comply with current regulations as well as for comprehensive assessment purposes.

SAEs associated with study procedures are to be notified using the same reporting procedure as described above.

In addition, if occurring after the end of the subject's follow-up period defined for this study (i.e. 30+/-3 days after the last procedure of vascular embolization), serious adverse and/or unexpected events that the Investigator thinks may be related to the mixture must be reported to Guerbet regardless of the time between the event and the end of the study.

According to local requirements, the investigator and Guerbet or its representatives will communicate relevant safety information to the appropriate agency(ies), IRB/IEC and/or all active investigators, as it becomes available.

In cases of serious adverse events, the Investigator and Guerbet shall forward their reports after due analysis, to the Chairman of the Ethics Committee, Licensing Authority (DCGI office) and Head of Institution where the trial has been conducted within 14 calendar days of occurrence of the serious adverse event.

The transmission of the information to Guerbet does not release the investigator from his responsibility to inform the regulatory authorities.

10.3 Pregnancy and Adverse Events of Special Interest

In addition to the above AEs, the special situations described below should be handled with the same procedure as the SAE reporting procedure.

10.3.1 Pregnancy

Any pregnancy (with or without an Adverse Event of women participating in the study and partners of men participating in the study) that occurs during the study must be reported to Guerbet and to the IRB/IEC via the SAE Report Form

Any participating subject who becomes aware of a pregnancy (subject's or subject's partner) during study participation should inform immediately the investigational site. The female subject should be immediately withdrawn from the mixture administration.

Pregnancy will be followed until completion or termination through pregnancy report form. If the pregnancy continues to term, the outcome (health of infant up to 8 weeks of age) will be reported to Guerbet. Any complication of pregnancy will be reported as an AE or SAE, as appropriate.

10.3.2 Adverse Events of Special Interest

An AE of Special Interest (AESI) is an AE designated by Guerbet for transmission to Pharmacovigilance in the same time frame as an SAE.

There are no AESI defined for this study.

11 PREMATURE DISCONTINUATION OF THE STUDY

11.1 Premature Discontinuation of the Study as per Guerbet Decision

Guerbet reserves the right to discontinue the study at any time for medical, administrative or other reasons.

Guerbet will inform the relevant authorities in India, the ethics committees, the investigational sites, pharmacists and hospital authorities according to the regulatory texts in force.

11.2 End of Study Participation for a Subject

End of study participation for a subject should be the end of follow-up for all subjects with at least one administration of mixture of Lipiodol® Ultra Fluid and surgical glue

Criteria for premature discontinuation of subjects:

- Inclusion criteria not met / Non inclusion criteria met
- Adverse Event (according to the investigator's judgement)
- Withdrawal of subject's consent
- Discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- At the discretion of the investigator if the subject safety or well-being is not compatible with study continuation
- Cancellation of the scheduled study procedure using Lipiodol® Ultra Fluid associated with surgical glues
- Lost–to-follow-up
- Other reason to be specified

For discontinued subjects, all data available at the time of their premature discontinuation will be reported in the medical file and the CRF (e.g. enrolment data, safety data, administration data if any, reason for discontinuation). The investigator must make every effort to collect and record all follow-up safety information (i.e. adverse events), unless the subject withdraws consent for further data collection for the study.

Discontinued subjects will receive appropriate medical care decided with the treating physicians for their condition.

12 STATISTICAL ANALYSIS

The following section summarizes the statistical analysis method, which is fully described in the Statistical Analysis Plan. Only descriptive statistics will be used to report all data collected in the study.

Quantitative variables will be summarized in tables including sample sizes, means, standard deviations and extreme values as well as medians and percentiles when appropriate.

Qualitative variables will be described in terms of frequencies and percentages of the number of individuals considered.

12.1 Subjects Included in the Analysis

Two subject sets will be defined in the study:

- All Included Set (AIS): this is the target set consisting of all subjects enrolled in the study and having signed the informed consent. This set will be used for describing demographic data, medical history and concomitant medication, unless otherwise noted.
- Treated set will consist of all AIS subjects receiving at least one injection of the mixture of Lipiodol® Ultra Fluid and surgical glues, regardless of the quantity. This set will be used for describing demographic and baseline data, extent of exposure and all safety and efficacy parameters.

12.2 Demographic and Baseline Data

Descriptive statistics will be calculated for age, body weight, height, sex, characteristics of the indication for the procedure (number of lesion, type and location), subjects' medical history, therapeutic/palliative strategy at enrolment (previous procedure and the next type of procedure planned, with Lipiodol® Ultra Fluid or not), concomitant medications at enrolment (treatments and pre-medications) .

Subjects' medical history will be coded using the MedDRA dictionary and tabulated by body system, preferred term and status (current or past).

Concomitant medications will be coded using the WHODrug dictionary and tabulated by ATC codes.

12.3 Safety Data

Extent of exposure data will be summarized per patient, per procedure and if necessary per administration: Number of procedures, reason for having a second procedure, subject duration of participation, number of injections, total volume and ratio of mixture, volumes of Lipiodol® Ultra Fluid and of the glues will be calculated, glues brand name, punctures sites, catheter flush done, other embolization material used and duration from first injection up to the time leaving the catheterization laboratory.

Concomitant medication, material and procedures administered during the subject participation will be summarized: Concomitant medications, additional embolization material introduced during study procedures and any new therapeutic/palliative procedure reported at follow-up will be

summarized. Concomitant medications will be coded using the WHODrug dictionary and tabulated by ATC codes.

Safety variables collected for this study are the following; descriptive statistics will be performed on these data.

For the primary evaluation criterion, the following parameters will be described on adverse events related to the mixture (ADRs) occurring per study procedure(s):

- Number and percentage of subjects experiencing at least one ADR
- Number and percentage of ADRs
- Number and percentage of subjects experiencing at least one serious ADR
- Distribution by System Organ Class and preferred term (MedDRA Dictionary): number and percentage of subjects experiencing at least one ADRs and number and percentage of ADRs
- Number and percentage of ADRs according to their intensity and outcome
- Number and percentage of subjects treated for an ADR
- Number and percentage of subjects with mixture administration withdrawal due to ADRs

For the secondary evaluation criterion, ADRs descriptions will be repeated with all ADRs occurring in the whole subject participation period (Study procedure (s) and follow-up period).

Adverse events parameters will be collected as described in section 10.1.3 during the study procedure(s) and during the follow-up period.

For the secondary evaluation criteria related to AEs, all parameters will be described (secondary safety criteria):

- Number and percentage of AEs
- Number and percentage of subjects experiencing at least one AE
- Distribution by System Organ Class and preferred term (MedDRA Dictionary): number and percentage of subjects experiencing at least one SAEs and number and percentage of SAEs
- Distribution by System Organ Class and preferred term (MedDRA Dictionary): number and percentage of subjects experiencing at least one AEs and number and percentage of AEs
- Number and percentage of AEs according to their intensity, outcome, action taken (with IMP and other)
- Number and percentage of AEs related to the mixture (ADRs), AEs related to study procedure and AEs both related to the mixture and related to study procedure.
- Number and percentage of subjects treated for an AE
- Number and percentage of subjects with mixture administration withdrawal due to an AE

12.4 Efficacy Data

Descriptive statistics will be summarized on all available efficacy data using the treated set and per lesion.

- Number and frequency of the target obliteration scores defined before any procedure

- Number and frequency of the post-procedure obliteration scores (including for the lesions not targeted initially)
- Number and frequency of lesions embolization matching target.

12.5 Handling of Missing Data

No imputation process will be used for missing data, descriptive statistics will be performed all on available data.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 References

The study will be conducted in accordance with the following regulatory / guidance texts:

- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, June 1964, and amended in: October 1975 (Tokyo), October 1983 (Venice), September 1989 (Hong Kong), October 1996 (Somerset West), Scotland, October 2000 (Edinburgh), 2002 (Washington), 2004 (Tokyo), October 2008 (Seoul), October 2013 (Fortaleza)
- Indian GCP guidelines as defined by Central Drugs Standard Control Organisation (CDSCO)
- DCGI Order F. No. GCT/20/SC/Clin./2013 of November 19, 2013
- Appendix XII of Schedule Y- "Compensation in case of injury or death during Clinical Trial" of Drugs and Cosmetics (Amendment) January 30th 2013
- Drugs and Cosmetics (Sixth Amendment) Rules, December 12th 2014
- Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies
- Directive 2010/84/EU from 15 December 2010 amending, as regards pharmacovigilance,

13.2 Institutional Review Board/Independent Ethics Committee and Regulatory/Competent Authorities

As per Indian regulation, the study may be initiated after having received the approval by and Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the authorization by the national Regulatory/Competent Authority. The final written approval and authorization must be available for a given participating site when initiating the study conduct at this particular site. Amongst all documents required locally, the approval and authorization must be obtained for the protocol, SmPC, the subject informed consent form and any other written information or document to be provided to the subjects.

In case of modifications to the study protocol, subject informed consent form or any other written information provided to the subjects, or to any study procedure; the modified documents will be submitted to IRB/IEC and Regulatory/Competent Authority opinions. Modifications may be implemented when the final approval and authorization are available.

In case of an emergency situation when the subject's safety may be at risk, Guerbet may implement emergency safety measures prior to obtaining IRB/IEC approval and Regulatory/Competent Authority opinion. In parallel to implementing these measures, Guerbet will immediately notify the concerned IRB/IEC and Regulatory/Competent Authorities of such implementation.

The documentation related to the approvals and authorizations must be filed in the Study Master File at Guerbet and at the participating sites in their respective Investigational Site File.

Notifications of Serious Adverse Events/Reactions to IRB/IEC and Regulatory/Competent Authority will be made according to the national requirements. Safety reporting is described in Section 10 of the present protocol.

13.3 Subject Informed Consent

Prior consent of subject should be taken for audio-visual recording of informed consent process and the same should be documented by the investigator. Prior to participation, all subjects must confirm their free and voluntary willingness to participate in the study. This confirmation is obtained in writing after having received a full oral and written explanation on the study and must be video recorded, as per Indian regulation:

- Aims and duration of the study;
- Collection of subject's data, their utilization for the study and confidentiality considerations;
- Potential benefits, foreseeable risks and inconveniencies related to the study;
- Rights and responsibilities of subjects, with particular emphasis on the right to refuse study participation or to withdraw consent to participation at any time without consequences or penalties;
- Information on Lipiodol® Ultra Fluid, surgical glues and their administration;
- Contact details of persons dedicated to the study at the site.

The language used when informing the subjects and answering their questions must be as understandable as possible and shall not induce any misunderstanding or feeling to be influenced to participate. Subjects must be given ample time to decide whether they agree to participate or not.

Subjects may consent to participate after having received all necessary information and all satisfactory answers to their questions. Their consent must be confirmed in writing by dating and signing the informed consent form(s) approved by the corresponding IRB/IEC and video recorded.

When the consent may not be directly obtained in writing, a legal representative/impartial witness may be involved in the process and confirm in writing that the subject consented freely and voluntarily.

The information of subjects may only be conducted by qualified site personnel, whose involvement and responsibility for subject information has been fully documented and approved by the Principal Investigator.

Completion of consenting procedures must be reported in the subject's medical file

The Principal Investigator must ensure that local applicable regulations/requirements are fully observed by the staff under her/his responsibility.

In case of modifications of the subject informed consent form or of any other document to be provided to the subjects, the IRB/IEC approval must be obtained prior to implementing the new document(s). Subjects who already consented may be asked to confirm their willingness to continue participating in writing. In any case, the same information and consent process as described above must be followed.

13.4 Study Records and Archiving

During the course of the study, sites must ensure completeness and accuracy of the study records that are to be filed in the Study Site File (SSF) provided by Guerbet or its delegate at the initiation visit. The completeness and accuracy of such files will be checked regularly by Guerbet representative (Clinical Research Associate or Monitor). The final check will occur at the close out visit when site participation is over.

At the end of the study, sites must ensure the SSF will be archived in an appropriate way that allows timely access and proper retention of documents. Retention period will be of at least 15 years after study completion. Guerbet will notify the sites in writing when study documents are no longer needed for retention.

14 QUALITY CONTROL / QUALITY ASSURANCE

14.1 Direct Access to Source Data/Documents

The investigator will allow Guerbet representatives, the persons responsible for audits, the representatives of the Ethics Committees and of the Regulatory Authorities to have direct access to source data/documents.

The investigator must guarantee the safety of the study data in the medical files by implementing security measures to prevent unauthorised access to the data.

The investigator undertakes, in accordance with the regulation in force, to make anonymous any subject data before collection by Guerbet. Especially the name and address of the subject will be deleted from any medium such as CRF, document for biological results, angiography images or digital supports.

If computerised medical files are used, the investigator must:

- At the start of the study, to print, sign and date all the medical files of all subjects,
- During the study, to print, sign and date in real time each data entry and each data change,
- In case printing of files is not possible, the computerized system must be validated and access should be granted to Guerbet or its representative.

14.2 Clinical Monitoring

Before the study is conducted at a given site and until the study is completed/terminated at the same given site, Guerbet will mandate a representative to perform a close monitoring of the study conduct that will ensure that the site is properly equipped; the staff is adequately experienced and knowledgeable of regulatory and ethical requirements.

The representative will perform regular site visits and report all discussions, subject and administration of the mixture of Lipiodol® Ultra Fluid and surgical glue data verification performed with particular attention to subject safety and well-being and study data accuracy and completeness.

The representative will check the accurate completion of the written informed consent for each subject. Video recording of each individual consent procedure will not be checked in order to ensure subject's privacy rights protection.

14.3 Clinical Data Handling

14.3.1 Data Reported in the CRF

An electronic CRF (eCRF) will be designed to allow recording of all the data required by the protocol.

The investigator or the designated person from his/her team agrees to complete the CRF/eCRF and all other documents provided by Guerbet and to reply to any data clarifications raised in a timely manner.

The investigator must attest:

- The authenticity of the data collected in the eCRF;
- The consistency between the data in the eCRF and those in the source documents, with the exception of data recorded directly in the eCRF and considered as source data.
- It will be acceptable to report efficacy data directly onto the CRF therefore considered as source document.

14.3.2 Data Reported in the CRF according to Subject Status

For subjects discontinued before the administration of the mixture, only the demographic data, eligibility assessment, the safety data and the reason for withdrawal will be reported.

For subjects with at least one administration of mixture was done, a safety follow-up at one month is expected to be done and all data available collected except the subject withdraws consent for further data collection/participation for/in the study.

14.3.3 Data Management System

A validated clinical data management system will be used for data process and data storage.

Data processing and control will be closely managed by Guerbet.

14.4 Audits and Inspections

At any time during the study conduct, Guerbet may mandate a representative to perform an audit of sites in order to assess compliance with the regulatory and ethical requirements, the study protocol and related instructions and to assess the accuracy and completeness of data generated by the sites.

In parallel, at any time during the study conduct, Competent/Regulatory Authorities may also carry out an inspection in the facilities of Guerbet and/or the sites. Guerbet will inform all the investigators immediately upon notification of a pending inspection. Likewise, the investigators will inform Guerbet of any pending inspection.

Whether for an audit or for a regulatory inspection, Guerbet and the sites both agree to cooperate in full transparency, confidentiality and professional secrecy.

The investigator must allow the representatives of Guerbet (audit) and/or of the Competent/Regulatory Authorities (inspection):

- To inspect the site, facilities and study material,
- To meet all members of his/her team involved in the study,
- To have direct access to study data and source documents,
- To consult all of the documents relevant to the study.

16 REFERENCES

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17 COMPANY LIABILITY INSURANCE

Guerbet's liability, as well as the liability of the investigators participating to this study, is covered by an insurance policy, a copy of the certificate being submitted to the investigator.

Furthermore, Guerbet and the investigator undertake to comply with the locally applicable legal requirements with respect to insurance, such as the appendix XII of Schedule Y-"Compensation in case of injury or death during Clinical Trial" of Drugs and Cosmetics (Amendment) Rules of January 30th 2013 and Drugs and Cosmetics (Sixth Amendment) Rules, December 12th 2014.

However, Guerbet and its insurer reject all liability in the following cases, which are merely indicative and not exhaustive:

- An accident due to a cause other than the mixture of Lipiodol® Ultra Fluid and surgical glue administered,
- An accident occurring during administration of the mixture of Lipiodol® Ultra Fluid and surgical glue used differently from the instructions given in the study protocol,
- An accident occurring for a subject whose consent to participation was not adequately collected.