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Protocol No. GDX-44-008

Proof of Concept study concerning efficacy of P03277 MR Imaging in HCC diagnosis

Phase IIa Clinical Study

Design

Multicenter, exploratory, non randomized, open label, two cohorts, two doses, phase IIa study

EudraCT No.: 2016-002930-62

IND No.: 123673

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Confidentiality clause

STUDY SYNOPSIS

Study Title:

Proof of Concept study concerning efficacy of P03277 MR Imaging in HCC diagnosis

Protocol No: GDX-44-008

Study product: P03277 [redacted]	**Active ingredient:** P03277
EudraCT number: 2016-002930-62	**IND Number:** 123673

Participating countries (Number of sites):

Minimum 2 sites in France

Study objectives

Primary objective:

To evaluate the diagnostic value for hepatocellular carcinoma (HCC) of P03277 in patients with suspected small nodules and chronic liver disease.

Secondary objectives:

To evaluate multiple quantitative and qualitative efficacy parameters and the safety (clinical and biological) profile of P03277 following single administration in suspected HCC patients

Study Design and methodology

Multi center, exploratory, non randomized, open label, two cohorts, two doses, phase IIa study.

Number of Subjects / Sample size

In total 40 subjects will be included in this exploratory study:

- Firstly, 30 subjects in a first cohort with a P03277 dose of 0.1 mmol/kg
- Then 10 subjects in a second cohort with a P03277 dose of 0.05 mmol/kg

Site selection:

The site should have appropriate expertise in liver MR imaging as well as clinical facilities. Investigators should have experience in conducting clinical studies and medical staff should have appropriate level of training.

Eligibility criteria

Selection/inclusion criteria :

1. Female or male adult subject aged at least 18 years old or older (subject having reached legal majority age).
2. Subject able and willing to participate to the study.
3. Subject having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any study related procedure being conducted.
4. Subject presenting with liver cirrhosis or chronic liver diseases as shown by previous liver biopsy or by combination of clinical, endoscopic, biological, ultrasound parameters, and elastography
5. Subject presenting with one to a maximum of 3 untreated hepatic nodule(s) of less than or equal

to 3 cm (long axis) previously identified and/or characterized through enhanced CT and/or MRI within a maximum of 21 days before P03277 imaging, confirmed for HCC or not

6. Female subject must be using a medically approved contraception method* detailed below or be surgically sterilized or post-menopausal (>12 months amenorrhea)

** medically approved contraception methods include: female sterilization, barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository), use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception, placement of an Intrauterine Device (IUD) or Intrauterine System (IUS).*

7. Subject affiliated to national health insurance according to local regulatory requirement

To be selected and included in the study, the subject must meet all these inclusion criteria.

Non-selection/non-inclusion criteria

1. Pregnant or breast-feeding female subject (a female subject of childbearing potential or with amenorrhea for less than 12 months must have a negative urine or serum pregnancy test within 24 hours prior to study MRI)
2. Subject presenting with hepatic nodule more than 3 cm in addition to nodule(s) less than or equal to 3 cm
3. Subject already treated for HCC by surgery or thermal ablation for which the resection or coagulation area is less than 2cm from the new nodule(s)
4. Subject previously treated by transarterial chemoembolization
5. Subject with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m2) based on measurement done or available within the 7 days before P03277 administration and assessed after any iodinated contrast agent administration, or with dialysis end stage renal disease (ESRD)
6. Subject with known class III/IV congestive heart failure according to the New York Heart Association classification
7. Subject having received or is scheduled to receive any contrast agent within 7 days before P03277 planned administration date and within 3 days after P03277 planned administration date.
8. Subject with known contra-indication(s) to the use or with known sensitivity to drugs from a similar pharmaceutical class as P03277
9. Subject having received any investigational medicinal product within 7 days prior to P03277 planned administration date
10. Subject presenting with any contraindication to MRI examination (see recommendations of the French Society of Radiology)
11. Subject having planned palliative/treatment interventions for the suspected nodules (radiotherapy, chemotherapy or others) during the study period except for biopsy/surgery
12. Subject related to the investigator or any other study staff or relative directly involved in the study conduct

13. Subject previously enrolled in this study
14. 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 in the study.
15. Subject unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the study).
16. Vulnerable subject according to article L1121-6 of the French Public Health Code,
17. Subject under guardianship or unable to give his/her consent according to the article L1121-8 of the French Public Health Code

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

Investigational Medicinal Product administration:

One single injection of P03277 to be administered with a power injector as an IV bolus at 2 mL/sec followed by a 0.9% saline flush at the same injection rate:

- at a dose of 0.1 mmol/kg for the first cohort (30 subjects),
- at a dose of 0.05 mmlo/kg for the second cohort (10 subjects).

Study duration

Subject participation duration could be from 2 days up to 3 months approximately

- The maximal period between subject screening and P03277 administration in the trial is 7 days but can be the same day if eGFR measurement within the last 7 days is available.
- Subject inclusion will be confirmed the day of administration with P03277 according to the eGFR results and urinary pregnancy test if applicable
- Subject will be followed up at +1 day safety visit
- Optionally and according to standard of care for histology analysis locally, the subject will have a specific biopsy or a surgically resected specimen collected at the time of loco-regional treatment. This procedure, whatever the type (biopsy, surgery), should be done between 3 days after P03277 administration and 13 weeks maximum. Alternatively it is acceptable to record results from histology done within 2 months prior to P03277 administration.

The study will be considered as completed once all the images collected for all the subjects will have been reviewed by expert readers.

Imaging Protocol

1.5 T and 3T MR equipments will be accepted. The same machine for each site should be used all along the study. Automatic real time bolus tracking will be used.

Standard Axial MR sequences will be used for pre-injection and post injection imaging.

- **Unenhanced imaging sequences**:

- GRE T1 in- and opposed-phase sequence
- 3D GRE T1 sequence with fat saturation
- FSE T2 sequence with fat saturation (can be done after injection)

- **Contrast-enhanced imaging sequences** - Post P03277 injection

- 3D GRE T1 sequences with fat saturation acquired during 3 time-points i.e. during arterial

(bolus track synchronization), portal (approx. 70-80 sec post injection) and delayed (3 minutes post injection) phases
- 3D GRE T1 sequences with fat saturation acquired at 15 ±5 minutes
- 3D GRE T1 sequences with fat saturation will be performed at 20mn, 1hour and 2 hours post-injection for the first 5 subjects and then possibly extended to next subjects if significant liver parenchyma enhancement is depicted.

Evaluation criteria:

Primary criteria:

- **Nodule diagnosis at P03277 imaging** (HCC, not HCC specify) will be assessed:
  - on a maximum of 3 hepatic nodules per subject
  - based on visual qualitative analysis of P03277 triphasic imaging (arterial, portal and delayed imaging) showing HCC typical hallmarks according to EASL/EORTC criteria (arterial hypervascularization and portal wash-out or delayed wash-out)
  - by two expert readers. In case of discordance, a consensus diagnostic will be obtained
- **The standard of reference** for diagnosing liver nodules (HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain) will be assessed by the site according to their standard of care and according to adapted EASL/EORTC diagnostic criteria, considering previous contrast enhanced imaging (CT and/or MRI) and/or histology analysis and/or the more recent AFP measurement available:
  HCC will be considered when:
    - Histology is positive for HCC
    - Or nodule identified and characterized by typical features using two different triphasic contrast enhanced modalities. Typical features are arterial hypervascularization and portal wash-out or delayed wash-out
    - Or AFP>200ng/mL in a presence of a single nodule

  Other diagnosis than HCC could be based on imaging only and/or histology.

Secondary criteria:

Secondary criteria will consist of both efficacy and safety evaluations in participating subjects:

Secondary efficacy criteria *(by on-going on-site and/or expert reading)**:***

- **Technical adequacy of images** *(on going on-site and expert reading*): adequate, yes/no and reason for inadequate recorded (artifact due to subject, artifacts due to the machine, artifacts due to contrast agent, injection technical failure, other specify)
- **Visualization of biliary and liver vascular abnormalities** *(expert reading)*: presence of portal thrombosis, hepatic venous thrombosis, biliary tract invasion, and visualization of arterio-portal fistula.
- **Number of liver nodules detected** *(on going on-site and expert reading)*
- **Qualitative evaluation** *(expert reading)*
  - At each phase (unenhanced, arterial, portal, delayed, 15 ±5 minutes): nodule (maximum of 3) intensity relative to parenchyma according to the scale: hypointense, hyperintense or isointense (and relative to spleen on T2 if hyperintense); In addition nodules will be described as homogeneous or heterogeneous
  - Presence of fat and Iron within liver nodules at unenhanced in and opposed phase GRE sequence
  - Visualization (yes/no) of a perilesional capsule at portal or delayed phase or at 15 ±5

minutes

- **Quantitative evaluation** *(on going on-site):*
  - At each phase, (unenhanced, arterial, portal, delayed, 15 ±5 minutes) SI measurement using ROIs placement in nodule (maximum of 3), liver, and background for SNR, CNR, percentage of nodule enhancement (PE)
  - On arterial and on portal phase, SI measurement of the aorta and the portal vein maximum vessel enhancement for SNR calculation purpose
- **Qualitative evaluation** *(expert reading)* for each available very delayed images (20mn, 1h, 2h) of any liver enhancement (hyperintense, isointense, hypointense) relative to the unenhanced fat-suppresssed GRE T1 sequence and of nodule enhancement relative to parenchyma.

Clinical and biological safety criteria:

- **For screening purpose,** the subject will have physical examination (performed by a physician), vital signs (systolic and diastolic blood pressure in supine position, pulse rate), eGFR measurement locally if not available within 7 days before P03277 administration. Urine or blood sample for pregnancy test for women with childbearing potential should be done within 24 hours prior to study MRI.

The following evaluation will be done during the subject participation:

- **Vital signs** (blood pressure, pulse rate): Before P03277 administration, 30 +/- 5 min after drug administration, and at Day +1 for all subjects
- **Biochemistry tests** by central lab at screening visit or inclusion visit and after P03277 administration at Day+1 for all subjects: sodium, potassium, chloride, random glucose, Blood Urea Nitrogen (BUN) / urea, creatinine, eGFR, Cystatin C, total protein, calcium, phosphorus, total bilirubin, conjugated bilirubin, unconjugated bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Lactate DeHydrogenase (LDH), Triglycerides (TG).
- **Hematology tests** by central lab at screening visit or inclusion visit and after administration at Day+1 for all subjects : Red Blood Cells (RBCs), White Blood Cells (WBCs), neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, Mean red blood Cells Volume (MCV).
- **Tolerance at the injection site** will be recorded from time of administration of P03277 up to 30 minutes post administration and 1 day after injection.
- **Adverse event (AE)** will be recorded throughout the subject participation until the +1day safety FU. Only AE that the investigator considers as related to P03277 and/or the study procedures will be recorded at the optional Visit 4 between 3 days after P03277 administration up to 3 month.

Statistical methods:

For primary endpoint: descriptive analysis of P03277 MRI sensitivity and specificity results using standard of reference will be presented by dose.

Descriptive statistics will be provided for secondary efficacy endpoints will be presented by dose and clinical and biological safety and will presented by dose and overall.

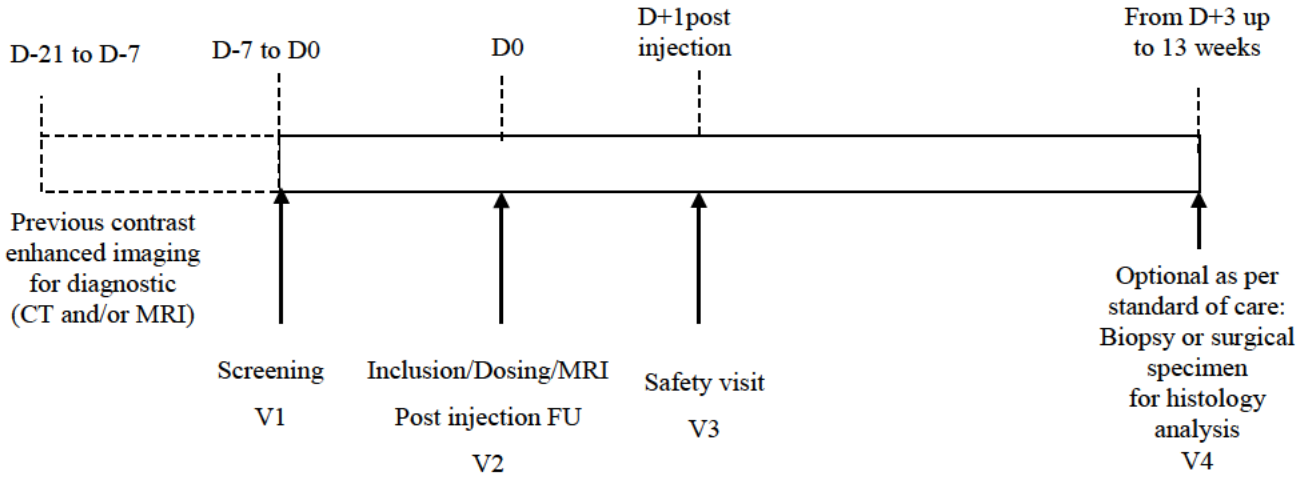
STUDY FLOW CHART

Visit	Screening (V1)	Inclusion and P03277 liver imaging visit (V2)						Safety follow-up (V3)	Biopsy /procedure for specimen histology (V4 optional as per standard of care)
Timing	-7 to -0 days	Inclusion Day 0	Pre-injection	Dosing	Acquisition of triphasic MRI sequences	30mn	Optional very delayed acquisition	Day +1	Between 3 days after V2 and up to 13 weeks
Informed consent signature	x								
Eligibility criteria (1)	x	x							
Physical examination (2)	x								
Demographic data	x								
Medical history	x								
Chronic liver disease status	x								
Previous imaging results and AFP measurement collected for reference diagnosis	x	x							
Proposed diagnosis according to available examinations for standard reference (excluding histology and P03277 images)								x	
Biopsy histologic analysis for reference diagnosis (3)									x
Body weight		x							
Concomitant treatments	←	—	—	—	—	—	—	→	
Pregnancy test (4)	~~x~~	x							
Vital signs (BP, HR) (5)	x	x				x		x	
Blood samples for laboratory parameters (6)	(x)	x						x	
e-GFR for screening (7)	x								
IP administration				x					
MRI examination (8)			x		x		(x)		
Injection-site tolerance (9)				←	—	→		x	
Adverse events (AEs) (10)	←	—	—	—	—	—	—	→	(x)

(1) Inclusion criteria checked at the screening visit must be confirmed at the inclusion visit.
(2) Physical examination should be performed by a physician: examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information indicating the global assessment (normal or abnormal (specify) of the physical examination should be recorded on source documentation.
(3) It is acceptable to record results from histology done within 2 months prior to P03277 administration
(4) Urinary or serum pregnancy test for woman of childbearing potential to be performed at inclusion. Results must be negative to continue in the trial.
(5) Vital signs (blood pressure, pulse rate).

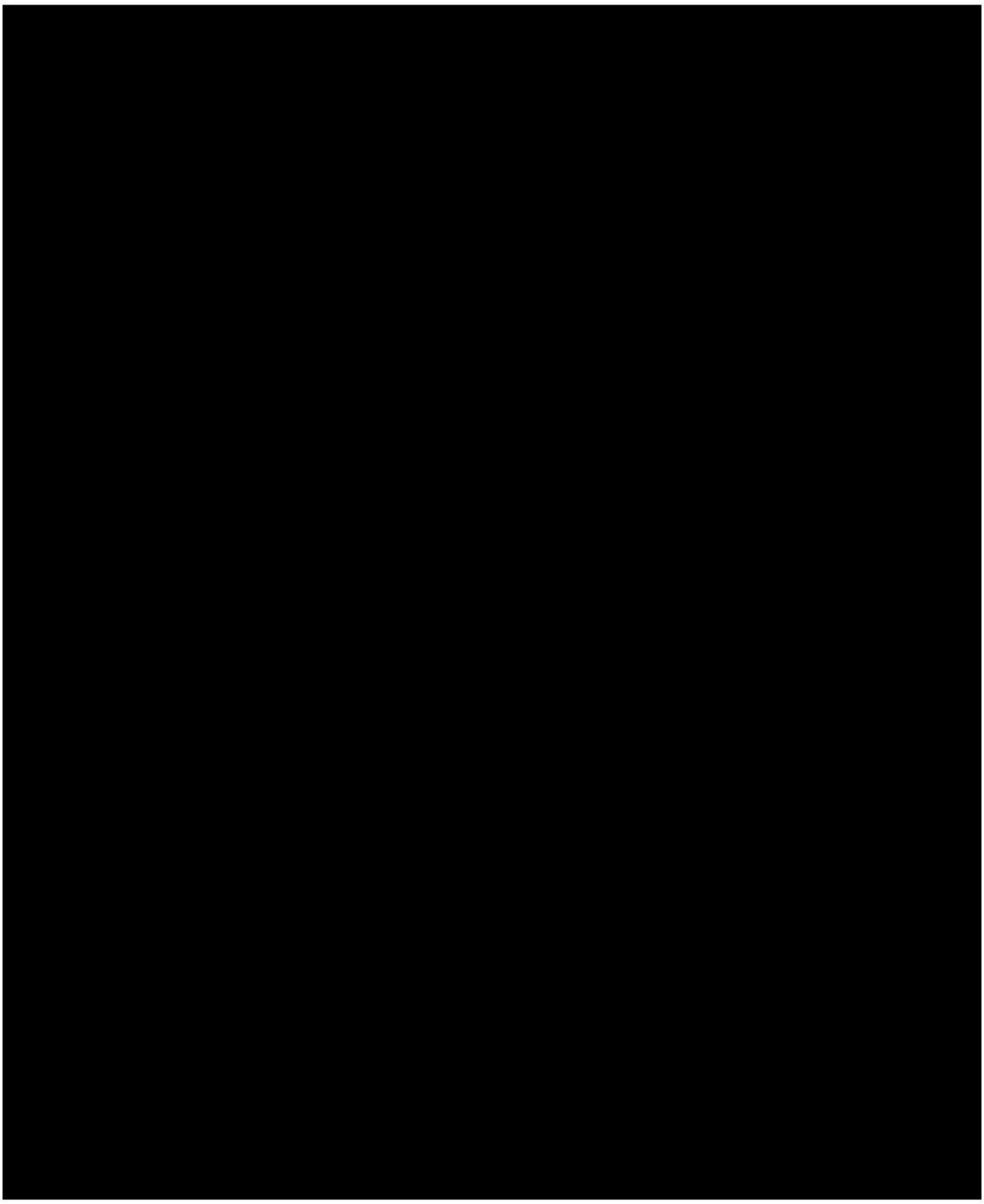
(6) Biochemistry and hematology tests to be done by central lab. Baseline can be done at screening or inclusion visit.
(7) e-GFR to be done by local Lab, and results must be available prior to administration of P03277
(8) MRI examination includes unenhanced sequences and triphasic post-injection sequences (arterial, portal, delayed, 15 ±5 minutes). Very delayed sequence will be performed at 20mn, 1hour and 2 hours post-injection for the first 5 subjects and then possibly extended to next subjects if parenchyma enhancement is visualized
(9) Injection-site tolerance monitoring is to be assessed from injection up to 30 minutes post injection and then at day +1 after administration.
(10) AEs will be assessed beginning with subject's informed consent signed and will end after the last follow up evaluation at day+1 after injection, and /or over a longer period if the investigator becomes aware of an adverse reaction/serious adverse reaction. At the time of optional visit 4, adverse event considered as related to the product/to the study should be reported in the study database.

STUDY DIAGRAM



The maximum duration of the study for the subject will be 14 weeks.

The study will be considered as completed once all the images collected for all the subjects will have been reviewed by expert readers.



ABBREVIATIONS

AE	Adverse Event
AFP	Alpha fetoprotein
AR	Adverse Reaction
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BW	Body Weight
CA	Competent Authority
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
CNR	Contrast to Noise Ratio
DSMB	Data Safety Monitoring Board
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
Gd	Gadolinium
eGFR	estimated Glomerular Filtration Rate
GMP	Good Manufacturing Practice
GRE	Gradient Echo
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INV	Investigator
IRB	Institutional Review Board
ISF	Investigator Site File

ITT	Intent ToTreat
IV	Intravenous
LDH	Lactate Dehydrogenase
LSO	Last Subject Out
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean red blood Cells Volume
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
PE	Percentage enhancement
PR	Pulse Rate
PT	Preferred Term
RBCs	Red Blood Cells
ROI	Region Of Interest
RT	Recovery Time
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SE	Spin Echo
SI	Signal Intensity
SNR	Signal to Noise Ratio
SOC	System Organ Classes
Subject ID	Subject IDentification
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analogic Scale
WBCs	White Blood Cells

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AMENDMENT N°2

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[redacted]

[redacted]

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1. INTRODUCTION AND STUDY RATIONALE

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide in men (554,000 new cases in 2012) and the ninth in women (228,000 new cases in 2012) and the second cause of cancer death responsible for more than 746,000 deaths in 2012 (1).

The dual arterial-portal blood supply is one specific complexity for the hepatic vascularization. The liver has a unique dual blood supply, with a compensatory relationship existing between the two sources so that the arterial flow increases when the portal venous flow decreases. HCC are highly vascular tumors and derive neovasculature through the process of angiogenesis. Multiphasic contrast enhanced computed tomography scan (CT), magnetic resonance imaging (MRI) or ultrasound (US) allow evaluation of the liver during both the arterial and the portal venous phases of contrast enhancement and therefore have become important modalities for the detection and characterization of HCC.

Surveillance program have changed the spectrum of HCC by depicting more small HCCs than before. For example, in Japan, HCC less than 2cm represented 4.6% of the cases between 1976 and 1985 and 33.1% between 1996 and 2000 (2). Diagnosis of mall HCCs is more difficult because they are less typical and may mimic benign lesions (3). On the contrary to lesions more than 3 cm, the specificity of diagnosing small HCC raises imaging specificity issues because of false positive cases corresponding to arterio-venous shunts, benign lesions or to other nodules (4). Dynamic characteristics with high intensity at arterial phase accompanied by a wash-out at portal or delayed phase are considered highly specific for HCC (5).

Gadolinium-Based Contrast Agents (GBCAs) have been used extensively in a large range of indications in MRI examinations. GBCAs consist of the active substance gadolinium (Gd) and a chelating agent. They can be categorized by their chemical structures into linear and macrocyclic agents and further subdivided by their charge (ionic or non-ionic). *In vitro* experiments have shown that the macrocyclic compounds are the most stable, with an undetectable release of Gd^{3+} ions under physiological conditions.

For multiphasic MRI, GBCA were found to participate to the characterization of malignancy of nodules in the liver. Extracellular GBCA are used for their ability to show typical characteristics for HCC with 0.820 (95% CI50.776, 0.857) of sensitivity in patients with any-sized lesions; and estimated specificities were 0.934 (95% CI50.881, 0.964) according to a recent meta-analysis (6).

P03277 is a new chemical entity discovered and developed by Guerbet. It is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in human, by intravenous administration, as a contrast agent for MRI.

P03277 has a molecular weight of 970.11 g/mol. [redacted]. P03277 is used as an aqueous injectable solution for injection at a concentration of 0.5 M.

[redacted]

The ability of P03277 to be a MR contrast agent has been demonstrated by at least two-fold higher T1 relaxivity compared to other available GBCAs. A proof of concept has been obtained for the efficacy of P03277 as a MR contrast agent for CNS imaging in a model of brain tumor (C6 glioma) implanted in rats. In this experimental brain tumor model, the dose of 0.1 mmol/kg of P03277 allowed for an increase in contrast enhancement of at least 30% as compared to other GBCAs administered at dose of 0.1 mmol/kg, including MultiHance® (highest relaxivity among the GBCA).

P03277 is a Gd chelate with a very high stability, limiting the risk of release of toxic free Gd in the body. The results of preclinical data indicate a good tolerance and a low toxicity profile at dose levels and exposure much higher than the anticipated clinical dose. This satisfactory tolerance has been confirmed in a phase I/IIa study. In this study, 36 healthy volunteers and 12 patients were administered with a single dose of P03277 and 18 volunteers with placebo. No serious adverse reaction occurred in any of these volunteers at any of tested dose at 0.025, 0.5, 0.75, 0.1, 0.2, and 0.3 mmol/kg BW. No clinically significant changes in vital signs or laboratory findings were noted.

In this phase I/IIa study, pharmacokinetics profile was shown to be dose-dependent (linear) that is the reason why only one dose is considered as needed for this new proof of concept study. [redacted]

The aim of GDX-44-008 study is to explore the diagnostic value for HCC of P03277 triphasic imaging of suspected nodules in patients with liver diseases. Some small HCC usually showing atypical features may be better seen and characterized under imaging with P03277. Participating subjects will not directly benefit from P03277 MRI. They will be diagnosed according to a combination of examinations for standard of reference including imaging and/or histology analysis

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the diagnostic value (specificity and sensitivity) for hepatocellular carcinoma of P03277 in patients with suspected small nodules and chronic liver disease.

2.2 Secondary Objectives

To evaluate multiple quantitative and qualitative efficacy parameters and the safety (clinical and biological) profile of P03277 following single administration in suspected HCC patients

2.3 Sub-Study / Ancillary Study Objectives

Not applicable

3. STUDY DESIGN

3.1 Protocol Description

Dual center, exploratory, non randomized, open label, two cohorts, two doses, phase IIa study.

The standard of reference for diagnostic will be given by the site according to their standard of care and adapted from EASL/EORTC diagnostic criteria (7) and considering previous contrast enhanced imaging (CT and/or MRI) and/or biopsy specimen analysis given on-site and/or the more recent AFP results available.

3.2 Study Duration

Subject participation duration could be from 2 days up to 3 months approximately

- The maximal period between subject screening and P03277 administration in the trial is 7 days but can be the same day if eGFR measurement within the last 7 days is available.
- Subject inclusion will be confirmed the day of administration with P03277 according to the eGFR results and urinary pregnancy test if applicable
- Subject will be followed up at +1 day safety visit
- Optionally and according to standard of care for histology analysis locally, the subject will have a specific biopsy or a surgically resected specimen collected at the time of loco-regional treatment. This procedure, whatever the type (biopsy or surgery), should be done between 3 days after P03277 administration and 13 weeks maximum. Alternatively it is acceptable to record results from histology done within 2 months prior to P03277 administration.

The study will be considered as completed once all the images collected for all the subjects will have been reviewed by expert readers.

3.3 Interim Analysis

Not applicable

3.4 Study Committee(s)

Not applicable

4. SUBJECT SELECTION

4.1 Inclusion Criteria

1. Female or male adult subject aged at least 18 years old or older (subject having reached legal majority age).
2. Subject able and willing to participate to the study.
3. Subject having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any study related procedure being conducted.
4. Subject presenting with liver cirrhosis or chronic liver disease as shown by previous liver biopsy or by combination of clinical, endoscopic, biological, ultrasound parameters, and elastography
5. Subject presenting with one to a maximum of 3 untreated hepatic nodule(s) of less than or equal to 3 cm (long axis) previously identified and/or characterized through enhanced CT and/or MRI within a maximum of 21 days before P03277 imaging, confirmed for HCC or not
6. Female subject must be using a medically approved contraception method* detailed below or be surgically sterilized or post-menopausal (>12 months amenorrhea)

   **medically approved contraception methods include: female sterilization, barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository), use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception, placement of an Intrauterine Device (IUD) or Intrauterine System (IUS).*
7. Subject affiliated to national health insurance according to local regulatory requirement

To be selected and included in the study, the subject must meet all these inclusion criteria.

4.2 Non Inclusion Criteria

1. Pregnant or breast-feeding female subject (a female subject of childbearing potential or with amenorrhea for less than 12 months must have a negative urine or serum pregnancy test and within 24 hours prior to study MRI).
2. Subject presenting with hepatic nodule more than 3 cm in addition to nodule(s) less than or equal to 3 cm
3. Subject already treated for HCC by surgery or thermal ablation for which the resection or coagulation area is less than 2cm from the new nodule(s)
4. Subject previously treated by transarterial chemoembolization
5. Subject with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m2) based on measurement done or available within the 7 days before P03277 administration and assessed after any iodinated contrast agent administration, or with dialysis end stage renal disease (ESRD)
6. Subject with known class III/IV congestive heart failure according to the New York Heart Association classification

7. Subject having received or is scheduled to receive any contrast agent within 7 days before P03277 planned administration date and within 3 days after P03277 planned administration date.
8. Subject with known contra-indication(s) to the use or with known sensitivity to drugs from a similar pharmaceutical class as P03277
9. Subject having received any investigational medicinal product within 7 days prior to P03277 planned administration date
10. Subject presenting with any contraindication to MRI examination (see recommendations of the French Society of Radiology)
11. Subject having planned palliative/treatment interventions for the suspected nodules (radiotherapy, chemotherapy or others) during the study period except for biopsy/surgery
12. Subject related to the investigator or any other study staff or relative directly involved in the study conduct
13. Subject previously enrolled in this study
14. 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 in the study.
15. Subject unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the study).
16. Vulnerable subject according to article L1121-6 of the French Public Health Code,
17. Subject under guardianship or unable to give his/her consent according to the article L1121-8 of the French Public Health Code

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

4.3 Subject Identification

After having signed their written informed consent, the subjects will be allocated an Identification Number (Subject ID).

Once the subject satisfies to all inclusion/non-inclusion criteria, they will be included in the study.

This Subject ID will be unique and will contain 6 digits: the first two digits corresponding to the country number, the following two digits corresponding to the site number, which are attributed at the beginning of the study, and the last two digits being chronologically implemented depending on subject enrollment. The lowest enrollment number will correspond to the first subject enrolled at this site and the highest number to the last subject enrolled.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

Investigational Medicinal Product(s) (IMPs) will be manufactured, labeled, packaged and released in accordance with:

- European Directive 2003/94/EC laying down the principles and guidelines of Good Manufacturing Practice in respect of Medicinal Products for human use and Investigational Medicinal Products for human use
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products

In addition, the IMP manufacturing, packaging, labeling and release will comply with any local applicable regulatory requirement.

The IMP will consist of an individually packaged vial in a carton box with a single use detachable label that will allow ensuring accuracy of IMP allocation per subject.

5.1 Investigational Medicinal Product: P03277

Name: P03277 [redacted]

Pharmaceutical form: vial of 20 ml

P03277 is an aqueous solution. Each vial contains 20 mL of solution presented as a sterile, clear, yellow, ready-to-use solution for injection.

Concentration: 0.5 M

P03277 dose per administration:

- 0.1 mmol/kg BW (corresponding to 0.2 mL/kg body weight) for the first cohort (30 subjects),
- 0.05 mmol/kg BW (corresponding to 0.1 mL/kg body weight) for the second cohort (10 subjects).

P03277 will be injected via a peripheral vein (the antecubital vein is preferred). The IV injection line will consist of a large bore indwelling catheter (at least 18 gauge).

Sufficient IMP must be allocated to one subject according to his/her body weight.

Route and method of administration: by intravenous (IV) bolus injection at 2 mL/s rate without dilution, followed by a 0.9% saline flush at same rate to ensure complete injection of the contrast medium.

The P03277 administration is to be performed by power injector in order to better control injection rate.

Please refer to the Investigator Brochure for more information on P03277.

5.2 Packaging, Labeling, Storage

Packaging and labeling will be performed in strict accordance with the local regulatory specifications and requirements.

The packaging and labeling of P03277 will be performed by Guerbet (or its designee).

In addition to the usual and regulatory labeling for clinical studies, each IMP will have a white detachable sticker indicating the protocol number, IMP number and other locally required information. This label will be stuck on the subject file or study documentation.

IMP will consist in a box that contains one 20 ml vial of P03277

All IMPs will be stored in a secure place, under the responsibility of the Investigator or other authorized individuals. The IMPs should be stored at a temperature of 25°C or below in the original package, protected from light and not frozen.

At the time of the study completion, all used (including empty vials) and unused IMPs should have been returned to the Sponsor or to the predefined location for storage before destruction.

5.3 Condition of Investigational Medicinal Product Allocation

5.3.1 Investigational Product(s) Allocation / Randomization

Since the study design is open label, IMP will not be allocated by randomization. Sufficient IMP(s) will be assigned to each investigational site. The Investigator will use the IMP with the lowest IMP number available at the site (chronological assignment). This number will be independent from the subject's identification number.

5.3.2 Double-Blind Conditions

Not applicable

5.3.3 Individual Study Treatment Unblinding

Not applicable

5.4 Investigational Medicinal Product Management

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense Investigational Medicinal Product(s) is responsible for ensuring that the IMP used in the clinical study is securely maintained as specified by Guerbet and in accordance with the applicable regulatory requirements.

Any quality issue noticed with the receipt or use of an IMP (deficient IMP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to Guerbet, who will initiate a complaint procedure.

Under no circumstances shall the investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

If during the administration of IMP, the subject experiences a Serious Adverse Event (SAE), the IMP administration must be discontinued and the subject rendered emergency medical care and monitored until the event is resolved (see section 10.2)

5.5 Non Investigational Medicinal Product(s) and Other Study Products

Not applicable

5.6 Study Product(s) 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 quantities of the IMP 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, including contraception, homeopathic products, over-the-counter medications, as well as prescription drugs, on-going at the time of subject's informed consent signed or administered during the study will be recorded in the subject CRF until safety follow-up visit (Day+1). The following information must be provided:

- Drug (brand name or generic name)
- Route of administration
- Purpose (Medical history/study disease/ AE/Premedication/contraception/Prophylaxis)
- Indication
- Duration of treatment

6.2 Concomitant Treatments of Special Attention

In order to limit any interference with the safety and efficacy evaluation of Investigational Product, the following precaution and restriction must be considered:

Currently, no treatment has been identified that is capable of preventing an allergic reaction with any gadolinium-based contrast agents. Thus, no pre-treatment of any nature will be recommended before contrast-enhanced MRI. Nevertheless, if the investigator decides to premedicate a subject, the treatment must be documented in the medical file and then in the CRF.

In general, there are no specific recommendations regarding Gadolinium-Based Contrast Agents, and therefore, no specific hydration procedure is defined in this protocol. Nonetheless, whenever possible, the subject should be encouraged to drink water and other non-alcoholic fluids liberally before and after the injection.

According to current knowledge, there is no other concomitant treatment of special attention in that study. However warnings and precautions for use of the concomitant treatments taken by the subject should be considered.

6.3 Prohibited Concomitant Treatments

Any other contrast agent should not be administered with 7 days before and 3 days after P03277 administration.

7. EVALUATION CRITERIA

An overview of the efficacy variables is provided in the Table 1: Overview of efficacy variables below.

Table 1: Overview of efficacy variables

Variables	On-going on-site Reading	Expert Reading
Primary efficacy variables		
Nodule diagnosis		✓
Secondary efficacy variables		
Technical adequacy of images	✓	✓
Number of nodules detected	✓	✓
Qualitative evaluation (nodule intensity, presence of intranodule iron and fat and visualization of perilesional capsule)		✓
Visualization of biliary and liver vascular abnormalities		✓
Qualitative evaluation at available very delayed image, liver enhancement relative to the unenhanced fat-suppressed GRE T1 sequence and nodule signal enhancement relative to parenchyma		✓
Quantitative evaluation SI measurements in nodules, liver, background, aorta and the portal vein for SNR CNR PE	✓	

7.1 Primary Criterion

For evaluation of **diagnostic value (defined as Sensitivity and Specificity) of P03277 for HCC** the following will be assessed:

Primary criteria:

- **Nodule diagnosis at P03277 imaging** (HCC, not HCC specify) will be assessed:
  - on a maximum of 3 hepatic nodules per subject
  - Based on visual qualitative analysis of P03277 triphasic imaging (arterial, portal and delayed phases) showing HCC typical hallmarks according to EASL/EORTC criteria (arterial hypervascularization and portal wash-out or delayed wash-out)
  - by two expert readers. In case of discordance, a consensus diagnostic will be obtained

- **The standard of reference** for diagnosing liver nodules (HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain) will be given by the site according to their standard of care and according to adapted EASL/EORTC diagnostic criteria, considering previous contrast enhanced imaging (CT and/or MRI) and/or histology analysis and/or the more recent AFP results available:
  HCC will be considered when:
    - Histology is positive for HCC
    - Or Nodule identified and characterized by typical features using two different triphasic contrast enhanced modalities. Typical features are arterial hypervascularization and portal wash-out or delayed wash-out

- Or AFP>200ng/mL in a presence of a single nodule

Other diagnosis than HCC could be based on imaging only and/or histology.

7.2 Secondary Criteria

7.2.1 Efficacy assessments of P03277 imaging

- **Technical adequacy of images** *(ongoing on-site and expert reading)* will be assessed as adequate, yes or no and reason for inadequacy will be recorded using-a 5 items (1= Artifacts due to subject , 2 = Artifacts due to machine, 3 = Artifacts due to contrast agent, 4 = Injection technical failure, 5 = Other, specify)
- **Visualization of biliary and liver vascular abnormalities** (*expert reading)* will be described: presence of portal thrombosis, hepatic venous thrombosis, biliary tract invasion, and visualization of arterio-portal fistula.
- **Number of nodules detected** *(ongoing on-site and expert reading)*
- **Qualitative evaluation** (*expert reading)*
  - At each phase (T2, T1 unenhanced, arterial, portal, delayed, 15 ±5 minutes): nodule (maximum of 3) intensity relative to parenchyma according to the scale: hypointense, hyperintense or isointense (and relative to spleen on T2 if hyperintense); In addition nodules will be described as homogeneous or heterogeneous
  - Presence of fat and Iron within the liver nodules at unenhanced phase in and opposed phase (intra nodule)
  - Visualization of a perilesional capsule (yes/no) at portal phase or delayed phase or at 15 ±5 minutes
- **Quantitative evaluation** *(ongoing on-site reading)*
  - At each phase, (T1 unenhanced, arterial, portal, delayed, 15 ±5 minutes) SI measurement on nodule (maximum of 3), liver, and background for SNR, CNR, and nodule percentage enhancement (PE)

    Nodule SNR (Signal to noise ratio) will be calculated at each phase using the following formula: SInodule/SDnoise where SI nodule is "nodule ROI intensity" and SDnoise is "Background ROI: SD intensity".

    CNR (contrast to noise ratio) will be calculated at each phase using the following formula: (SInodule-SIliver)/ SDnoise where SInodule is "nodule ROI intensity"; SIliver is "liver parenchyma ROI intensity" and SDnoise is "Background ROI: SD intensity".

    PE (Nodule Percentage Enhancement) will be calculated using the following formula: [(SIpost-SIpre)/SIpre)]*100 where SIpost is the nodule signal intensity at each phase (arterial, portal, delayed, 15 ±5 minutes) and SIpre is the nodule signal intensity at unenhanced sequence.

  - On arterial and on portal phase, SI measurement of the aorta and the portal vein maximum vessel enhancement for SNR calculation purpose.

    Vascular SNR (Signal to noise ratio) will be calculated using the following formula: SIaorta/SDnoise where SI aorta is "aorta ROI intensity" and SDnoise is "Background ROI: SD intensity" at arterial phase, SI portal vein/SDnoise where SI

portal vein is "portal vein ROI intensity" and SDnoise is "Background ROI: SD intensity" at portal and delayed phases and at 15 ±5 minutes

- **Qualitative evaluation** (*expert reading)* for each available very delayed images (20mn, 1h, 2h) for visualization of the parenchyma enhancement relative to unenhanced fat-suppressed GRE T1 sequence (hyperintense, isointense, hypointense) and nodule enhancement relative to parenchyma

7.2.2 Safety assessment

The safety assessments will be based on the following: Adverse Events (AEs), injection site tolerance, clinical laboratory parameters (blood), vital signs. A central laboratory will be used to analyze and report blood chemistry/hematology. eGFR would also have been evaluated locally only for screening. eGFR evaluated centrally will be used for safety evaluation.

- **Adverse events**

  Adverse Event monitoring will be recorded until Day+1. After, AEs that the investigator considers related to P03277 and/or study procedures will be recorded at optional V4.

- **Injection-site tolerance**

  For all subjects, injection-site tolerance (burning, pain, eruption, extravasation, inflammation, or other) will be assessed over 1 day following each contrast agent injection (during the injection up to 30 ± 5 mn, and the day after injection) and over a longer period if the investigator becomes aware of any related AE. In case of injection-site pain, the subject will be asked to specify the level of pain using a visual analogic scale (VAS, [redacted]) from 0 (no pain) to 10 (maximal pain).

- **Clinical laboratory parameters**

  For each subject, blood samples will be performed at baseline and Day+1 for being analyzed by a central laboratory.

  The following parameters will be obtained and assessed:

  - Hematology: Red Blood Cells (RBCs), White Blood Cells (WBCs), neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, Mean red blood Cells Volume (MCV).
  - Biochemistry: sodium, potassium, chloride, random glucose, Blood Urea Nitrogen (BUN) / urea, creatinine, eGFR, Cystatin C, total protein, calcium, phosphorus, total bilirubin, unconjugated and conjugated bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Lactate DeHydrogenase (LDH). Triglycerides (TG).

  In female subjects of childbearing potential, a urine or serum pregnancy test will be performed on-site prior to the administration of IMP.

  For all other laboratory assessments, the central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant as an AE or alternatively according to investigator's judgement as medical history if measured at baseline and related to an underlying disease.

- **Vital signs**

  Vital signs (systolic and diastolic blood pressure in supine position, pulse rate) will be measured and recorded according to the following schedules:

  - Immediately prior to each contrast agent injection (baseline value)
  - At 30+/-5 minutes following P03277 injection
  - One day after P03277 injection

  If significant changes in vital signs occur, vital signs should be recorded more frequently, and for as long as necessary, to ensure that the changes have been resolved and/or that the subject is stable. All clinically significant abnormal value or change value will be recorded as AEs or alternatively according to investigator's judgement as medical history if measured at baseline and related to an underlying disease.

  A significant clinically change is defined as follows: Pulse Rate < 40 or >100 bpm; systolic Blood Pressure < 90 or >160 mmHg; diastolic Blood Pressure > 100 mmHg.

  Blood pressure and pulse rate will be measured after a rest of 10 minutes in supine position. Blood pressure will not be measured on the arm used for the injection.

8. NUMBER OF SUBJECTS

As a proof of concept study, no statistical test is planned. Subjects' data will be analyzed with descriptive statistics investigating the potential efficacy of P03277 in the liver for the diagnosis of HCC, by dose.

In total 40 subjects will be included:

- Firstly, 30 subjects in a first cohort with a P03277 dose of 0.1 mmol/kg
- Then 10 subjects in a second cohort with a P03277 dose of 0.05 mmol/kg

Number of subjects for the first cohort of the study is based on the hypothesis supported by a meta-analysis of several publications (8) that among the 30 subjects with suspected nodules, around 66% would have a HCC and the remaining subjects would be negative (liver nodule proven as a non HCC) and or uncertain after biopsy. Those hypothetic figures would help to estimate sensitivity and specificity values with the limitations expected for such small sample size.

It is considered that 10 subjects included in the second cohort will be sufficient to have an exploratory evaluation of the diagnostic value based on sensitivity and specificity.

9. STUDY SCHEDULE AND PROCEDURES

9.1 Study Schedule

9.1.1 Screening Visit – Visit 1 – Day - 7 to Day 0

During this visit, the following tasks or assessments will be performed:

- A **written informed consent** will be obtained from the subject as described in Section14.3;
- The subject will be attributed an **Identification Number** as described in Section 4.3;
- A **routine physical examination** (performed by a physician) including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological; Information indicating the global assessment (normal or abnormal (specify)) of the physical examination should be recorded on source documentation;
- A review and record of **concomitant treatments**;
- Recording of **demographic data** such as sex, age, measurement of height, ethnic origin (self-reported race/ethnicity).
- **Documentation of relevant medical history**/current medical condition present before signing the informed consent. The Investigator will also question on any possible previous contrast agents injection intolerance (type of agent : iodinated, gadolinium complex, barium, radiopharmaceutical, other specify) and report them in medical history;
- **Documentation of chronic liver disease history and status**: documentation supporting the diagnostic of chronic liver disease (biopsy, endoscopic, biological, ultrasound parameters, and elastography), aetiology of chronic liver disease (alcohol, HBV, HCV, non-alcoholic-NASH, other specify) and last evaluation of Child Pugh score (see appendix 1) available (including the date);
- **Documentation of suspected nodules** detection modality and date;
- **Examination results available for standard of reference diagnosis evaluation** per nodule before P03277 administration:
  - Liver map (according to Couinaud segmentation) identifying the localization of the nodule(s) (maximum of 3) for standard of reference
  - Size of the nodule (s) to be considered according to investigator's choice among the several imaging modalities
  - Contrast enhanced imaging modalities used for characterization (CT and/or MRI), type of contrast agent used for MRI (extracellular, hepato-specific), date of acquisition and, for each of nodules if HCC typical hallmark is visualized according to EASL/EORTC criteria and in case of MRI using hepatospecific contrast agent, also if hyperintensity of parenchyma relative to the nodule is seen.
  - The more recent AFP measurements available and date
- **Biopsy or intervention for specimen surgery** scheduled for histology analysis. The planned date should be recorded.
- A **urine or serum pregnancy test** for all women of childbearing potential should be done and must be negative;
- **Verification of eligibility criteria**. Criteria relative to eGFR measurement may not be available at screening ;

- Schedule of **blood sample collection for serum creatinine** dosage if applicable, in order to obtain the results and calculate eGFR at the time of inclusion at the latest;
- If done at screening, **blood samples for baseline hematology/biochemistry tests** will be collected according to central laboratory manual. If not done at screening, they have to be scheduled at inclusion visit (V2).
- Recording the subject screening visit in the CRF.

9.1.2 Inclusion Visit – Visit 2 – Day 0

Inclusion visit can be the same day as screening if all eligibility criteria can be verified the same day.

During this visit, the following tasks or assessments will be performed:

- **Verification of inclusion and non-inclusion criteria** by the Investigator; creatinine results for eGFR calculation should be available before P03277 administration.
- **A urine or serum pregnancy test** for female subject of childbearing potential will be performed prior to P03277 administration and must be negative (do not perform the test if a negative pregnancy test result performed within 24 h prior to the MRI is available);
- Any changes in **concomitant treatments** since the last visit will be documented;
- **Any AE** occurred since the last visit will be documented
- If not already done at screening, **blood samples for baseline haematology/biochemistry tests** will be collected according to central laboratory manual;
- Measurement of **body weight**;
- **Vital signs** (systolic and diastolic Blood Pressure in supine position, Pulse Rate) will be recorded prior to contrast agent injection;
- One or two **IMP will be allocated** according to subject body weight;
- **The appropriate volume of P03277 will be administered** by IV as a bolus at the rate of 2 mL/second following a 0.9% saline flush at the same rate. The following information will be documented in the source document and reported on CRF pages: the location of the IV injection line, confirmation of power injector use and reason for not, actual volume injected and actual rate of the injection, and start time of injection, volume of saline flush, any reason for different rate than 2mL/s or different volumes of more than 10% than the calculated one;
- **Unenhanced and contrast-enhanced MRI** will be performed according to the required sequences specified in imaging protocol section 9.2. Enhanced imaging sequences will be acquired according to imaging protocol and start time of each post injection sequences will be recorded. Any deviation from the specified MRI procedures and the reason for it (scanner-related problem or subject-related problem) will be also documented;
- **Vital signs** (systolic and diastolic Blood Pressure and PR) will be obtained 30 ± 5minutes after the injection of P03277. If significant changes in vital signs occur, vital signs should be recorded more frequently and for as long as necessary, to ensure that the changes are resolved, and/or that the subject is stable;
- **Injection-site tolerance** (burning, pain, eruption, extravasation, inflammation, or other) is to be assessed during the injection and up to 30 minutes after the injection of P03277;

- **Assessment of AEs** will be documented;
- Safety follow-up visit (Visit 3) needs to be scheduled 1 day post P03277 injection.

9.1.3 Visit 3 – Day +1

During this visit, the following assessments or tasks will be performed:

- Use/change of **concomitant treatments** will be documented;
- **Blood samples for baseline haematology/biochemistry tests** will be collected according to central laboratory manual;
- **Vital Signs** (systolic and diastolic Blood Pressure in supine position, PR) should be recorded;
- **Injection-site tolerance** is to be evaluated;
- **Assessment of AEs** will be documented;
- **Proposed diagnosis as standard of reference** for each nodule (HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain) should be assessed according to available evaluations (excluding histology and P03277 images) .

9.1.4 Visit 4 – Optional (from 3 days up to 13 weeks)

Optionally, a biopsy will be done or surgically resected specimen will be collected at the time of loco-regional treatment and be analyzed for histology by local pathologist.

This procedure, whatever the type (biopsy or surgery), should be done between 3 days after P03277 administration to up to 13 weeks maximum. Aternativelly it is acceptable to record results from histology done within 2 months prior to P03277 administration.

- **Examination results available for standard of reference diagnosis evaluation**
  - Date of nodule material collection (2 dates maximum)
  - Histological diagnosis per nodule : HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain
- **Assessment of AEs that the investigator considers related to P03277 and/or study procedures.**

9.2 Imaging Protocol

1.5 T and 3T MR equipments will be accepted. The same machine for each site should be used all along the study. Automatic real time bolus tracking will be used.

Standard Axial MR sequences will be used for pre-injection and post injection imaging.

- **Unenhanced imaging sequences**:

- GRE T1 in- and opposed-phase sequence
- 3D GRE T1 sequence with fat saturation
- FSE T2 sequence with fat saturation (can be done after injection)

- **Contrast-enhanced imaging sequences** - Post P03277 injection:

- 3D GRE T1 sequences with fat saturation acquired during 3 time-points at arterial (bolus track synchronization), portal (approx. 70-80 sec post injection) and delayed (3 minutes post

injection) phases
- 3D GRE T1 sequences with fat saturation acquired at 15 ±5 minutes
- Additional 3D GRE T1 sequences with fat saturation will be performed at 20mn, 1hour and 2 hours post-injection for the first 5 subjects and then possibly proposed to next subjects if significant liver parenchyma enhancement is depicted.

9.3 On Site on going Reading of Images

For each investigational site, a radiologist expert in liver diseases will be appointed for on-site readings and provide on-site on-going reading results.

9.4 Expert Reading of Images

9.4.1 Manuals and Supplies

Guerbet will document the imaging tasks and obligations of the investigational site in a Site Imaging Manual. The standardized image acquisition guidelines will be provided to the sites as part of the Site Imaging Manual.

In addition, the Site Imaging Manual will detail the steps required for masking confidential subject information and transferring images to Guerbet.

Guerbet will document the expert imaging process in a Read Charter.

9.4.2 Site Qualification

Guerbet's monitors will perform pre-study site selection and site training. These contacts will ensure that the imaging protocol-stipulated can be performed by the site, are programmed and prepared prior to enrollment of the first subject and that the Site Imaging Manual will be accurately followed by the investigator.

9.4.3 Receipt, Tracking, Quality Check of Images

During the study, Guerbet will request that investigational sites send anonymous images of the subjects to Guerbet. Their format will be agreed prior to study start and defined in the Site Imaging Manual. Images will be tracked within Guerbet.

Guerbet will ensure that all imaging protocol requirements have been followed and will document this quality control.

9.4.4 Expert Readers training

Two expert radiologists will be appointed from the participating sites, having expertise in the interpretation of MR images from of liver diseases and HCC.

Before the expert readers start the readings, proper training will be delivered and documented according to the Read Charter.

Reading software at each site will be recorded.

9.4.5 Image assessments

After having received all the subject images acquired with P03277 for the study, Guerbet will be presenting them to expert readers.

A specific CRF will be set-up for experts reading entry.

Both experts will provide evaluation for qualitative evaluations of P03277 imaging according to the Read Charter.

9.4.6 Nodule mapping

Nodule tracking will be performed using a liver map according to Couinaud segmentation drawings completed on-site and by expert readers. The purpose is to guarantee an unambiguous assignment (matching) of the liver nodules between standard of reference and expert readings. Read charter will detail how nodule mapping will be organized.

9.4.7 Consensus meeting

In case of diagnostic discordance (primary criterion), a consensus meeting will be organized after nodule concordance. In this case the qualitative evaluations will be reviewed globally and may be modified.

9.4.8 Image Warehouse and Final Deliverables

All imaging data will be maintained in a secure environment. Guerbet will maintain a centralized image archive that will contain every imaging examination received from the clinical investigators for the study. Measurements will also be stored at reader site responsible for quantitative evaluation so that these data may be audited if necessary.

9.5 Other Centralized Study Procedures

9.5.1 Clinical laboratory parameters

A central laboratory will be used for all scheduled laboratory tests in this study except for the pregnancy test which will be done locally and eGFR which will be assessed locally (for screening) and centrally (for safety evaluation). The investigator will be provided with a list of normal ranges prior to the start of the study. The central laboratory will provide the necessary kits to collect the blood samples and will also provide appropriate information regarding shipping of the samples.

Care should be taken during blood sampling in order to avoid potential generation of false positive blood value (e.g., by inappropriate use of the tourniquet or forceful withdrawal of blood). Each original laboratory report will be filled with the subject's source document.

All laboratory reports must be promptly reviewed by the Investigator, and upon review, initialed and dated by the Investigator. Change(s) in post-dose test values considered clinically significant, which would require either additional control or therapy, must be documented in the subject's source document and, in case of disturbing or influencing factor(s) on values/samples, details of the appropriate value(s) and the source of disturbance or influence (e.g. quality of sample, co-treatment etc.) are to be recorded. All values considered clinically significant will be reported as AEs or alternatively according to investigator's judgement as medical history if measured at baseline and related to an underlying disease.

Laboratory samples obtained for this study will be used only for this study. Samples obtained in this study will not be retained or used for any other purposes.

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 patient or investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable 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 to the medicinal product.

Any disease identified and diagnosed by study contrast-enhanced MRI will not be considered as AE.

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 adverse events, whether considered as related or not to the Investigational Medicinal Product and/or the imaging procedure 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 adverse events occurring from ICF signature until Day+1, must be reported and followed even if no IMP was administered. The investigator shall document all adverse events in the medical file and the appropriate section of the CRF.

In addition, if occurring after the safety visit at Day+1, events that the investigator thinks may be associated with the study medication/procedure must be reported to the sponsor at the optional Visit 4 and further regardless of the time between the event and the end of the study.

Safety information to be collected by the investigator with the same procedure as adverse events: 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 an IMP, 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 this protocol, the overdose is defined as more than 0.3 mmol/kg for P03277. Any overdose, with or without adverse event, will be reported as AE and, in addition, on SAE form if the associated event is serious.

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 on 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 (i.e. last study visit), the subject should be followed-up until AE resolution or a justification should be provided by the Investigator (i.e. chronic disease) in the medical file.
- **Causal relationship to the Investigational Medicinal Product:**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no IMP has been administered (pre-administration period) or when no causal relationship exists between the study drug and the event, but an obvious alternative cause exists (e.g. the subject's underlying medical condition or concomitant therapy).
- **Causal relationship to a study procedure – appart from IMP:**
  - 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 IMP:**
  - No Action: for AE occurring during the pre-treatment/procedure or post-treatment/procedure period, or if the Investigational Medicinal Product dosing/administration remained the same in spite of AE being present.
  - Action taken :
    - No action
    - IMP withdrawn
- **Other action taken:**
  - AE-targeted medication: the subject took a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the CRF ("concomitant drug" section until V3).
  - 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 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 were 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 an investigational medicinal product, or would be sufficient to consider changes in the study drug administration or in the overall conduct of the study:

- Any post-study serious and/or unexpected adverse event that occurs after the subject has completed the study and that is considered as related to the Investigational Medicinal Product 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 or the development of the study drug such as:
    - A SAE which could be associated with the study procedures and which could modify the conduct of the study
    - A significant hazard such as an unusual failure in efficacy.
    - A new finding from a newly completed animal study.

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.

Also, any suspicion of transmission of an infectious agent via an IMP should be considered as a serious and processed as an SAE.

In addition, any adverse reaction resulting from an occupational exposure (i.e. exposition to IMP of an investigating site staff member) may be directly reported to Guerbet.

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, provided there is no aggravation of the disease to which it is related.
- Hospitalizations, which are not associated to an adverse event (such as hospitalization for check up).
- Any hospitalization planned for the biopsy specimen collection for histology analysis (biopsy, resection, liver transplantation and any treatment) as part of the standard of care of the HCC

10.2.2 Procedure for Reporting Serious Adverse Events

SAEs occurring from ICF signature until Safey visit at Day+1 are to be reported to Guerbet Pharmacovigilance department.

The investigator **must immediately** forward to Guerbet Pharmacovigilance department 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:

- **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)1 45 91 50 00.**

Additional information (e/g. autopsy, lab reports…) may be required by the Sponsor in a timely fashion to ensure accurate follow-up and assessment of each case and should be forwarded, anonymized, with a new form specifying basic information (follow-up number, subject details and number, adverse event, study product, causal relationship) and the new information.

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 age, sex and subject's study enrolment number
- Subject's medical history relevant to the assessment of the event
- Type of event by reporting a diagnosis or if not available, symptoms
- Date and time to onset of the event
- End date of the event (will be reported in a follow-up report if the event is still ongoing at the time of first notification)
- Name of the investigational drug or procedure, date and time of administration, dose and volume administered
- Causal relationship to the investigational drug or procedure (mandatory)
- Outcome at the time of reporting

Any event leading to a SAE report should be reported in the medical file and in the adverse event 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.

In addition, if occurring after the end of the subject's follow-up period defined for this study, events, serious or not, that the Investigator thinks may be associated with the study medication/procedure must be reported to the sponsor regardless of the time between the event and the end of the study.

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

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

The transmission of the information to the sponsor does not release the investigator from his responsibility to inform the regulatory authorities, if applicable.

10.3 Pregnancy and Adverse Events of Special Interest

In addition to the above adverse events, 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 and up to 7 days post P03277 administration must be reported to Guerbet 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 IMP administration.

Pregnancy will be monitored until completion or termination. If the pregnancy continues to term, the outcome (health of infant up to 8 weeks of age) will be reported to Guerbet using specific forms 'history and start of pregnancy" and "course and outcome of pregnancy" that will be provided by the pharmacovigilance. Any complication of pregnancy will be reported as an AE or SAE, as appropriate.

10.3.2 Adverse Events of Special Interest

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

The AESI for this protocol is the following: Nephrogenic Systemic Fibrosis (NSF).

10.4 Other important safety issue /New fact

Any safety issues that may alter the current benefit-risk assessment of an investigational medicinal product, or would be sufficient to consider changes in the study drug administration or would involve any update of study documents or in the overall conduct of the study should be evaluated by the sponsor. It includes any new event likely to affect the safety of the subjects and that may be related to the conduct of the study or the development of the study drug such as:

- A SAE which could lead to the modification of the conduct of the study
- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease (if applicable).
- A new major finding from an animal study,
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,
- Recommendations of the DMC, if any, where relevant for the safety of subjects,
- Any serious adverse reaction, expected or not, involving healthy volunteers.

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

It might require other action, such as:

- urgent safety measures and their notification

- substantial amendments
- early termination of the trial

10.5 Unblinding Procedures

Not applicable

11. PREMATURE DISCONTINUATION OF THE STUDY

11.1 Premature Discontinuation of the Study 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 each country, the ethics committees, the study site investigators, pharmacists and hospital authorities according to the regulatory texts in force.

11.2 End of Study Participation for a Subject

Screening failures: Subjects who signed the informed consent form and discontinue before P03277 administration will be considered screening failures.

Criteria for premature discontinuation of subjects:

- eGFR < 60 mL/min/1.73m2 at local blood sample screening;
- Adverse event (according to the investigator's judgment);
- Withdrawal of subject's consent;
- Subject lost to follow-up (date of last contact will be documented in the medical file and the CRF). Any effort will be undertaken to know the reason for this loss to follow-up and/or to exclude any adverse reaction as this reason. This will be documented in the medical file;
- Any treatment or medical procedure (e.g. chemotherapy, radiotherapy) during the study period;
- At the discretion of the investigator if the subject safety or well-being is not compatible with study continuation;
- Examination for standard of reference not available.

The data to be reported in the CRF for subjects subsequently discontinuing from the study are detailed in the protocol section 15.3.2.

Subjects prematurely discontinuing the study will be replaced. It is expected to have around 3 subjects

12. STATISTICAL ANALYSIS

The following section summarizes the statistical analysis method, which is fully described in the Statistical Analysis Plan.

12.1 Subjects Included in the Analysis

There will be four subject sets defined for this study: All subjects set, the Safety Set (SS), the Full Analysis Set (FAS) and the Per-Protocol Set (PPS).

All subject set will include all subjects with available data. This set will be used for subject disposition summaries and individual listings.

The Safety Set will include all subjects, receiving at least one injection of P03277, regardless of the quantity. This set will be used for evaluation of safety and description of demographic data and baseline characteristics.

The Full Analysis Set will include all subjects who undergone P03277 imaging and a standard of reference completed. This set will be used for evaluation of efficacy.

The Per Protocol Set will be a subset of the FAS and will include all subjects who have no major protocol deviations throughout their whole study period. Major deviations will be defined as having an impact on the primary efficacy criteria (e.g. P03277 wrong volume administered to the subject differing of more than 10% from the calculated one). Primary analysis will be repeated on this set.

12.2 Demographic and Baseline Data

Demographic parameters are age, sex, childbearing potential, body weight, height, and body mass index (BMI), ethnic origin (self-reported race/ethnicity). Baseline characteristics are the subject's history (including the medical history, intolerance history), the physical examination, chronic liver disease status at inclusion, documentation of suspected nodules, and the concomitant treatments on going at the time of screening/inclusion and before administration of P03277.

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height and BMI and displayed by dose and overall. Frequency and percentages will be calculated for sex, subject chronic liver disease status at inclusion, and concomitant treatments on going at the time of screening/inclusion and ended before administration of P03277. These parameters will be displayed by dose and overall.

Subject's medical history will be coded using the MedDRA dictionary and tabulated by dose body system, preferred term and status (concomitant or not) and presented overall as well.

Subject's concomitant treatments will be coded using the Anatomical Therapeutic Chemical (ATC) Drug dictionary and tabulated by dose ATC code and presented overall as well .

12.3 Efficacy Data

Efficacy data will be summarized and presented by dose using the FAS and PP set for primary efficacy analysis and only using FAS for any other efficacy analysis.

Primary efficacy analysis

First of all, results of **examinations results used for standard of reference** will be presented: at subject level showing number and frequency of AFP results by category (>200ng/mL or ≤200ng/mL) and by number of nodules for a subject (multiple or single nodule), previous contrast enhanced imaging modalities (CT and/or MRI), timelines and type of contrast agent category for MRI. At nodule level, typical imaging hallmark obtained by nodule (CT and/or MRI) and intensity of parenchyma relative to the nodule at each available phase will be presented. Timelines for biopsy (or surgical specimen collection) will be presented at subject level and nodules histology results (HCC, other malignant, regenerative or dysplastic nodule, benign, uncertain) will be presented at nodule level.

P03277 imaging diagnosis (HCC and not HCC) will be presented at nodule level displaying number and frequency for each standard of reference group HCC or not HCC according to the **Table 2.**

Table 2 : Diagnostic value evaluation for HCC

		P03277 imaging expert reading results		
		HCC: (Typical features on this MR examination)	Not HCC (No nodule/atypical features)	
Standard of reference	HCC:	True positive *n1*	False negative *n3*	Total *n1+n3*
	Not HCC including uncertain cases	False positive *n2*	True negative *n4*	Total *n2+n4*
		Total *n1 + n2*	Total *n3+n4*	All total *N+*

The following parameters will be calculated:

Sensitivity: the number of nodules showing true positive HCC divided by all nodules considered HCC according to standard of reference (*n1 / n1+n3*)

Specificity: the number of nodules showing true negative HCC divided by all nodules considered as not HCC or uncertain as standard of reference (*n4 / n2+n4*)

Accuracy: the number of nodules showing true positive HCC and true negative HCC over all nodules (*n1+n4 /N+)*

Positive predictive value: the number of nodules showing true positive HCC /all nodules showing HCC according to P03277 imaging (*n1 / n1+n2*)

Negative predictive value: the number of nodules showing true negative HCC /all nodules not showing HCC according to P03277 imaging (*n4 / n3+n4)*

Secondary efficacy analysis

Technical adequacy of images

Technical adequacy will be presented by reading type (on-site or expert reading), by displaying number and frequency of adequate and inadequate images and the categories for inadequacy.

Visualization of biliary and liver vascular abnormalities

Biliary and liver vascular abnormalities will be presented globally, by displaying number and frequency of portal thrombosis, hepatic venous thrombosis, biliary tract invasion, and visualization of arterio-portal fistula.

Number of nodules detected

Number of nodules detected will be presented at subject level, showing number [n], mean, standard deviation [SD], median, minimum, and maximum.

Qualitative evaluation of nodule intensity and nodule description

Qualitative evaluation of nodule intensity (hypointensity, hyperintensity, isointensity and hetero/homogeneous) relative to parenchyma at each phase as well as, presence of capsule, visualization of fat, and iron presence will be presented by displaying number and frequency for each standard of reference group (HCC or not HCC/uncertainty).

Quantitative evaluation of nodule intensity

Quantitative evaluations of nodule intensity (SI, SNR, CNR, and PE) will be presented for each standard of reference group (HCC or not HCC/uncertainty) by displaying number [n], mean, standard deviation [SD], median, minimum, and maximum.

Quantitative evaluation of vascular intensity

Quantitative evaluations of aorta intensity and portal vein intensity (SI and SNR) will be presented globally and for each standard of reference group of subjects (subject with at least HCC or subject without any HCC) by displaying number [n], mean, standard deviation [SD], median, minimum, and maximum.

Qualitative evaluation at very delayed sequences for visualization of the parenchyma enhancement and nodule description

Qualitative evaluations for visualization of the parenchyma enhancement will be presented globally showing number and frequency at three available very delayed images and sequences (20mn, 1h, 2h).
Qualitative evaluations for nodule enhancement relative to parenchyma will be presented by displaying number and frequency for each reference group (HCC or not HCC/uncertainty)

12.4 Safety Data

Safety analysis will be done using the safety set presented by dose and overall.

Extent of exposure

Duration between IMP administration and end of study, volume theoretically administered, volume actually administered, actual rate of administration, theoretical rate of administration will be tabulated.

Frequency tabulation of theoretical volume actually administered and theoretical rate of administration actually performed will be also displayed.

Adverse events

All analyses of AEs will be based on the number of subjects with AEs. Adverse events occurring after D+1 that the investigators considers as related to P03277 /study procedures will be included in this analysis.

Adverse events will be coded with the most recent version of MedDRA at the time of the database lock.

The time period for the assessment of AEs will be divided into 3 mutually exclusive and exhaustive periods: before administration of P03277, after administration of P03277 until day +1 FU and after safety follow-up until biopsy if it is done.

Events will be classified as treatment-emergent (TEAE) if they started or increased after P02377 administration. This will also include events with missing intensity.

Partial start dates/times will be queried. If information is not available to reliably allocate to a session and period, the allocation will be agreed at the data review meeting before database lock. If there is any doubt about treatment emergence, AEs will be classified as treatment emergent.

In all summaries, recurring AEs (AEs classified with the same preferred term) for a given subject in a given period will be counted as a single AE. If severity is summarized, this will be the maximum severity.

Overall overview

The number (%) of subjects having at least one Treatment Emergent AE (TEAE) as follows will be summarized for:

At least one TEAE
At least one adverse reaction (relationship to study treatment classified as 'Related')
At least one TEAE with action taken with study treatment
At least one TEAE with classifications of outcome

The table will show the same information for serious AE, defined as AEs with serious classified as 'yes' or missing.

The table will be repeated for all AEs

Distribution of AEs and SAEs

A table will be presented showing the total numbers of AEs and SAEs and the distribution of AEs (number [%] of subjects with 0, 1, 2 etc… AEs) . The table will also show the same information for SAEs defined as TEAEs with serious classified as 'yes' or missing, unless the number of SAEs make this uninformative.

Summaries by System Organ Classes (SOC) and Preferred Term (PT)

The table of summaries of at least one TEAE will be repeated by SOC only (without the breakdown by PT).

Concomitant medication after P03277 administration

Concomitant medications will be coded using the WHO Drug dictionary and be presented displaying number and frequency by ATC System Main Group and Therapeutic Subgroup.

Injection site tolerance

Number of subjects experiencing burning, pain, eruption, extravasation and inflammation at site injection will be tabulated. Pain at injection site will be measured using the Visual Assessment Scale (VAS) and VAS measurements for these subjects will be tabulated.

Laboratory data

The statistical analysis will present results in standard international units and United States units. Original units will be only listed. Laboratory data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of laboratory data to their reference ranges and according to their clinical significance. Quantitative analyses will be done by tabulating raw data and change from baseline. They will be displayed qualitatively as well as by means of shift tables.

Vital signs

Vital signs will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of vital signs data to their normal ranges (see section 7.2.2) and according to their clinical significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

12.5 Handling of Missing Data

No imputation or replacement of missing data will be carried out.

12.6 Interim Analysis

Not applicable

13. STUDY COMMITTEES(S)

The IMP used, in this study, as contrast agent belongs to a well-known product class (GBCA) and there is, a priori, no particular expected safety concerns. In addition, the P03277 has a linear pharmacokinetic profile similar to the other Gd chelates and the preliminary results obtained during the phase I study with several doses of P03277 showed no clinical and biological alert signal.

For all these reasons, an IDMC (Independent Data Monitoring Committee) has not been established for the study.

However, the safety data will be monitored during the study conduct.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 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)
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Good Clinical Practice E6 (R1) Current Step 4 version dated 10 June 1996
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A Current Step 4 version dated 27 October 1994
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials E8 Current Step 4 version dated 17 July 1997
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products

- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 11 on Electronic Records; Electronic Signatures
- French regulation :
    - Current version of the French Public Health Code
    - Decree 2016-1537 dated 16 November 2016 related to research involving human subjects
    - Loi n° 2004-806 du 9 août 2004 relative à la politique de santé publique
    - Loi n° 2002-303 du 4 mars 2002 relative aux « Droits des malades et la qualité du système de santé »
    - Loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés et la Loi n° 94-548 (1 juillet 1994) relative au traitement de données nominatives ayant pour fin la recherche dans le domaine de la santé. - Décret d'application n° 2005-1309 du 20 octobre 2005.
    - Méthodologie de référence pour les traitements de données personnelles opérées dans le cadre des recherches biomédicales (MR001), octobre 2010 modifiée 21 juillet 2016.
    - Bonnes Pratiques de Fabrication, Journal officiel de la République française du 7 janvier 2014, texte n°2 sur 82)

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

As per international regulation, the clinical study may be initiated only 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 investigational 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, investigator's brochure, 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 subjects' 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 investigational 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.

14.3 Subject Informed Consent

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:

- Aims, methodology and duration of the study;
- 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 IMP and its administration;
- Contact details of persons dedicated to the study at the investigational 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.

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 investigational site personnel, whose involvement and responsibility for subject information has been fully documented and approved by the Principal Investigator.

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 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.

14.4 Study Records and Archiving

During the course of the clinical study, investigational sites must ensure completeness and accuracy of the study records that are to be filed in the Investigator Site File (ISF) provided by Guerbet 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 investigational site participation is over.

At the end of the study, investigational sites must ensure the ISF 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 investigational sites in writing when study documents are no longer needed for retention.

15. QUALITY CONTROL / QUALITY ASSURANCE

15.1 Direct Access to Source Data/Documents

The investigator will allow Guerbet representatives, the persons responsible for the audit, 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 subjects will be deleted from any medium such as CRF, document for biological results, X-Ray films or digital supports.

For this study, the following will be considered as source data: expert reading data will be completed directly onto the CRF.

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.

15.2 Clinical Monitoring

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

The representative will perform regular investigational site visits and report all discussions, subject and IMP data verification performed with particular attention to subjects' safety and well-being and study data accuracy and completeness.

15.3 Clinical Data Handling

15.3.1 Data Reported in the CRF

The CRF will 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, at each subject visit, and all other documents provided by Guerbet (e.g. documents relating to the IMP management…) and to reply to any data clarifications raised in a timely manner.

The investigator must attest:

- The authenticity of the data collected in the CRF;
- The consistence between the data in the CRF and those in the source documents, with the exception of those data recorded directly in the CRF and considered as source data.

15.3.2 Data Reported in the CRF according to Subject Status

For screening failure, only the date of visit, date of informed consent signature, demographic data, physical examination, the adverse events and the reason for withdrawal will be reported. If the visit 2 was done without any P03277 administration, all data available at the time of withdrawal will be reported.

For subjects withdrawn from the study after the administration of the IMP, all data available at the time of withdrawal will be reported in the medical file and the CRF (e.g.: inclusion data, safety data, administration data, imaging data, reason for withdrawal…). The investigator must make every effort to collect and record all follow-up safety information (i.e., adverse events, injection-site tolerance, as appropriate), unless the subject withdraws consent for further data collection/participation for/in the study.

15.3.3 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's representative.

15.4 Audits and Inspections

At any time during the study conduct, Guerbet may mandate a representative to perform an audit of investigational 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 investigational 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 investigational sites. Guerbet will inform all the investigators immediately upon notification of a pending inspection. Likewise, the investigator will inform Guerbet of any pending inspection.

Whether for an audit or for a regulatory inspection, Guerbet and the investigational 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.

[redacted]

17. REFERENCES

1. IARC : Globocan 2012 : Estimated Cancer Incidence, Mortality and prevalence Worldwide in 2012
2. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisinaga Y, Hayashi K, Honda T, Kitabatake S, Kuzuya T, Nonogaki K, Kasugai T, Shimizu I, Changes in characteristics and survival rate of hepatocellular carcinoma from 1976 to 2000: analysis of 1365 patients in a single institution in Japan. Cancer.2004 1;100(11):2415-21
3. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso J.R, Boix L, Sala M, Varela M, Llovet J.M, Brú C, Bruix, J Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma, Hepatology 2008;47:97–104.
4. Mueller GC1, Hussain HK, Carlos RC, Nghiem HV, Francis IR. Effectiveness of MR Imaging in Characterizing Small Hepatic Lesions: Routine Versus Expert Interpretation 2003;180(3):673-80
5. Jordi Bruix, Maria Reig, and Morris Sherman, Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma, Gastroenterology 2016;150:835–853
6. Joanna K. Duncan, Ning Ma, BMa,Thomas D. Vreugdenburg, Alun L. Cameron and Guy Maddern, Gadoxetic Acid-Enhanced MRI for the Characterization of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis J. MAGN. RESON. IMAGING 2016 Jun 14. doi: 10.1002/jmri.25345. [Epub ahead of print]
7. European Association for Study of Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer 2012;48:599-641.
8. Yoon Jin Lee, Jeong Min Lee, Ji Sung Lee, Hwa Young Lee, Bo Hyun Park, Young Hoon Kim, Joon Koo Han, Byung Ihn Choi, Hepatocellular Carcinoma: Diagnostic Performance of Multidetector CT and MR Imaging—A Systematic Review and Meta-Analysis

18. 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.

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 investigational medicinal product administered,
- An accident occurring during use of the investigational medicinal product differently from the instructions given in the study protocol,
- An accident occurring for a subject whose consent to participation was not adequately collected.

19. APPENDICES

19.1 Child-Pugh Classification of Severity of Liver Disease

Child-Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Total Bilirubin, mg/dL	</= 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time Prolongation (s)	<4.0	4-6	>6.0
Encephalopathy	None	Grade 1-2	Grade 3-4

Class	Points
A: well-compensated disease	5-6
B: significant functional compromise	7-9
C: decompensated disease	10-15

[redacted]