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 CONFIDENTIAL	Protocol No. GDX-44-004 Version No. 2.0 (Protocol including amendment n°1) Date: 11 July , 2016	<div style="background-color: black; width: 100px; height: 15px; margin-bottom: 5px;"></div> Page 1 / 84
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<p style="text-align: center;">Protocol No. GDX-44-004</p> <p style="text-align: center;">P03277 Dose Finding Study in Central Nervous System (CNS) Magnetic Resonance Imaging (MRI)</p> <p style="text-align: center;">Phase IIb Clinical Study</p>

Design:

Multi-center, double-blind, randomized, controlled, parallel dose groups, cross-over design with comparator

EudraCT No.: 2014-003576-23


IND No.: 123673

<p>INTERNATIONAL COORDINATOR</p> <div style="background-color: black; width: 260px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 345px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 745px; height: 15px;"></div>
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STUDY SYNOPSIS

Study Title: P03277 Dose Finding Study in Central Nervous System (CNS) Magnetic Resonance Imaging (MRI) Phase IIb Clinical Study	
Study Product(s): P03277 XXXXXXXXXX XXXXXXXXXX	Active Ingredient(s): P03277
EudraCT No.: 2014-003576-23	IND No.: 123673
	Participating countries (Number of sites): Worldwide study involving approximately 40 centers
Study Objectives <u>Primary objective:</u> To determine a safe and effective dose of P03277 based on the Contrast to Noise Ratio (CNR) when comparing with Gadobenate Dimeglumine (MultiHance®) at 0.1 mmol/kg body weight (BW). <u>Secondary objectives:</u> <ol style="list-style-type: none"> To assess technical adequacy of images To evaluate capacity of lesion detection To evaluate diagnostic information using lesion visualization variables (lesion border delineation, internal morphology and degree of contrast enhancement) To evaluate diagnostic confidence To compare overall diagnostic preference between P03277 and MultiHance® To assess P03277 dose / response relationship for CNR and lesion visualization variables To evaluate the impact of P03277 and MultiHance®-enhanced MRI on subject treatment plan To assess the safety profile of P03277 as compared to MultiHance® after intravenous administration 	
Study design and methodology Multi-center, double-blind, randomized, controlled, parallel dose groups, cross-over design with comparator. The Investigational Medicinal Products used during the study are P03277 and MultiHance®. Two subsets of subjects will be included in the study: <ul style="list-style-type: none"> ➤ The first subset will include the first subject of each study center. Subjects will be administered at 0.05 or 0.1 mmol/kg BW of P03277 and MultiHance®, 0.1 mmol/kg BW. Images from this subset of subjects will be used to provide training images for the independent blinded off-site readers, to ensure that the imaging protocol/acquisition sequences has been appropriately programmed, and that the MR images produced can be transferred to the core laboratory. Consequently, these subjects will not be included in the efficacy analysis but only for the safety assessment. ➤ The second subset will be composed of all subjects (except the first one of each site) selected by the sites. Subjects will be administered at 0.025, 0.05, 0.1, 0.2 mmol/kg BW of P03277 and 	

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0.1 mmol/kg BW of MultiHance®.

The subjects will be randomly assigned to one of the doses of P03277 and to one series of 2 MRIs performed each at two study visits separated by a wash out period of 2 days minimum up to 14 days. The series are related to the use of contrast agent: one series will have P03277 at visit 2 and MultiHance® at visit 4 or vice versa for the other series.

The randomization scheme will allocate subjects to the two P03277 treatment arms in a 1:1 ratio for the first subset of subjects and to the four P03277 treatment arms in a 1:1:1:1 ratio for the second subset of subjects. The P03277 will be injected at a rate of 2 mL/second.

The same dose of MultiHance®, 0.1 mmol/kg BW by single IV injection at a rate of 2 mL/second, will be injected to all subjects.

The investigator and the subject will remain blinded to IMPs allocation (nature of the IMPs and order of the IMP injection) as well as the dose of P03277 used. A designated unblinded site staff member will be in charge of preparation and administration of the IMPs.

For the second subset of subjects, randomization will be stratified via IWRS by the following stratification factor: presence of brain metastasis (yes/no). Subjects with brain metastasis will be included at a minimum of 20%. MRI images will be evaluated on-site, by investigators and off-site by 3 independent blinded readers. Contrast to Noise Ratio will be evaluated by 3 independent blinded readers and will serve as primary efficacy results.

To allow exact matching of lesions throughout the different imaging sequences and the two MR examination with P03277 and MultiHance®, an independent radiologist (lesion tracker) will perform lesion tracking based only on the available CNS diagrams, separate from the investigator image and independent blinded reader image evaluations.


The IWRS will be used to record subjects visits and allocate IMPs i.e., screening (visit 1), inclusion/first MRI (visit 2), second MRI (visit 4), safety visits (visit 3 and visit 5) and at any time to record screening failure (prior randomization) and premature study discontinuation (after randomization).

For both subsets of subjects, safety will be assessed using vital signs, 12-lead ECGs, injection site tolerance, clinical laboratory parameters (blood and urine) and by adverse events (AEs) monitoring.

Number of subjects / sample size

Based on the hypothesis below, a total of 280 subjects will be enrolled in the study:

- First subset: maximum 40 subjects (depending on the number of participating sites) on the basis of 1 subject per site.
- Second subset: 240 subjects based on the following assumption: the study aims at detecting a minimum of 30% increase of CNR for at least one of the four tested dose of P03277 compared to control arm MultiHance® at dose of 0.1 mmol/kg BW. A sample size of 50 evaluable subjects per group is required to obtain a power of at least 90%, using a t-test of a normal mean difference with a 1-sided significance level of 0.025 (Holm's step-down method in a Multiple Comparisons Design) and a common standard deviation of 3.01. Therefore, a minimum of 50 evaluable subjects per dose group and a minimum of 200 evaluable subjects in total will have to be enrolled in this study. It is anticipated that some of the subjects will not complete both MRI evaluations. To offset this, an additional 10 subjects per group will be added to the 50 required, resulting in a total sample size of a minimum of

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240. In addition, subjects with brain metastasis will be randomized at a minimum of 20% of the second subset of subjects (a minimum of 20% of subjects with brain metastasis per group of P03277 doses).

Eligibility criteria


Inclusion criteria:

1. Female or male adult subject (subject having reached legal majority age).
2. Subject presenting, at the time of inclusion, with known or highly suspected focal areas of disrupted Blood Brain Barrier (BBB) (e.g., primary and secondary tumors, focal inflammatory disorders) including at least one expected enhancing lesion of minimum 5 mm (long axis). This lesion must have been detected on a previous imaging procedure (computerized Tomography (CT) or MRI).
3. Subject scheduled for a routine CNS contrast-enhanced MRI examination for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the study.
4. Subject able and willing to participate to the study.
5. 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.
6. Subject affiliated to national health insurance according to local regulatory requirements.

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

Non-inclusion criteria:

1. Subject presenting with acute or chronic Grade III (at least) renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m² based on one eGFR assessment performed the day of the MRI prior to the first contrast agent injection.
2. Subject presenting with known class III/IV congestive heart failure according to the New York Heart Association classification (NYHA).
3. 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 and must be using a medically approved contraception method* until the last study visit).
4. Subject having received any investigational medicinal product within 30 days prior to study entry.
5. Subject previously enrolled in this study.
6. Subject presenting with any contraindication to MRI examinations.
7. Subject with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or other GBCAs.
8. Subject having received any contrast agent (MRI or CT) within 3 days prior to study products administration, or scheduled to receive any contrast agent during the course of the study and within 24 hours after the second study product administration.
9. Subject having received any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc...) within 7 days prior to the first MRI or expected/scheduled to have a change in any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc...) in-between the 2 MRI examinations.

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10. 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.
11. 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).
12. Subject related to the Investigator or any other study staff or relative directly involved in the study conduct.
13. Subject presenting with acute relapse of multiple sclerosis.

** 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).*

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

The diagnosis obtained from previous imaging examinations will be considered as medical history to assess inclusion criteria. All study analyses will be based only on the images obtained through the study MRIs.

Investigational Medicinal Product(s) administration

Study product 1:

P03277: single intravenous (IV) bolus injection at one of the following four doses (0.025, 0.05, 0.1, or 0.2 mmol/kg BW) at a rate of 2 mL/second.

Study product 2:

MultiHance®: contrast agent approved for CNS imaging, administered at the approved dose of 0.1 mmol/kg BW by single IV bolus injection at a rate of 2 mL/second.

Study duration

Minimum study duration for subjects: 4 days

Maximum study duration for subjects: 22 days

The study includes a maximum of 5 visits:

- One screening visit up to 7 days prior to inclusion (screening could be done the same day as the inclusion visit if all the inclusion/exclusion criteria are met)
- Two sequential imaging visits (minimum interval 2 days and up to 14 days): each visit will consist of a P03277 injection or MultiHance® injection and MRI procedure (if during the first visit the MRI procedure is performed with P03277 injection then the second visit will be done with MultiHance® injection and vice versa for the other series) .
- Two safety visits: 1 day after each injection and MRI examination.

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

Evaluation criteria

**Primary criterion:**

Contrast to Noise ratio (CNR) (for each of the 3 independent blinded readers evaluations (off-site read))

Signal Intensity (SI) measurements will be made in Region Of Interest (ROI) on the pre and post-injection, axial 3D T1 weighted Gradient Echo (GRE) for brain and sagittal T1-weighted Spin-Echo (SE) or Turbo Spin-Echo (TSE) for spine, image set. ROIs will be placed on a maximum of three visualized lesions in the largest conspicuous enhancing areas. CNR will then be calculated for each lesion according to the following equation:

$$CNR = \frac{SI_{lesion} - SI_{ht}}{SD_{noise}}$$

where,

SI_{lesion} = the SI in the Region of Interest (ROI) in the lesion

SI_{ht} = the SI in the ROI in healthy tissue (brain or spinal cord)

SD_{noise} = standard deviation of background noise.

The primary criterion is calculated by subject, and by independent blinded reader, in averaging the Contrast to Noise Ratio (CNR) for maximum 3 enhanced lesions. Only lesions which matched on both MRIs after lesion tracking will be used.

Secondary criteria:

1. Technical adequacy of images (on-site and off-site reads)

Images will be evaluated as adequate or not. Images are considered technically inadequate if artifacts completely compromise image interpretability.

2. Lesion detection capacity (on-site and off-site reads):

Number, size and location of lesions detected, and the presence or absence of enhancement will be recorded.

3. Diagnostic information using lesion visualization variables (on-site and off-site reads):

Three variables (lesion border delineation, internal morphology and degree of contrast enhancement) will be assessed on combined unenhanced and enhanced MRI on a 4-point scale.

○ Border delineation:


Delineation of the lesion border is defined as the distinction of lesion from surrounding tissues, structures, or edema; and the detection of extent of the lesion (for extra-axial lesions, this pertains to the definition of the space in which the lesion is present, and for intra-axial lesions, it pertains to the invasion of white matter, gray matter, or both; the neuroanatomical distribution of the lesion; and its mass effect).

○ Internal morphology:

Internal morphology of the lesion includes an identification of lesion architecture and the intra-lesion features such as necrosis, hemorrhage and vascularity.

○ Degree of contrast enhancement:

This criterion will be a qualitative visual assessment (not based on signal intensity measurement).

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4. Diagnostic confidence (on-site and off-site reads):


Diagnosis and diagnostic confidence will be recorded for each subject.

5. Overall diagnostic preference in a global matched-pairs fashion (off-site read).
6. P03277 dose / response relationship for CNR and lesion visualization variables.
7. Impact of contrast agent-enhanced MRI on subject treatment plan (on-site read).
8. Safety assessments: vital signs, 12-lead ECGs, injection site tolerance, clinical laboratory parameters (blood and urine) and adverse events (AEs) monitoring.

Statistical methods

Student t-test using Holm's step-down method in a Multiple Comparisons Design with 0.025 type-one error will be used to evaluate the dose-response of P03277 for each Independent Blinded Reader (IBR) with regards to the CNR value as the primary endpoint. The post-CNR value will be normalized by the pre-CNR value calculated on the same basis.

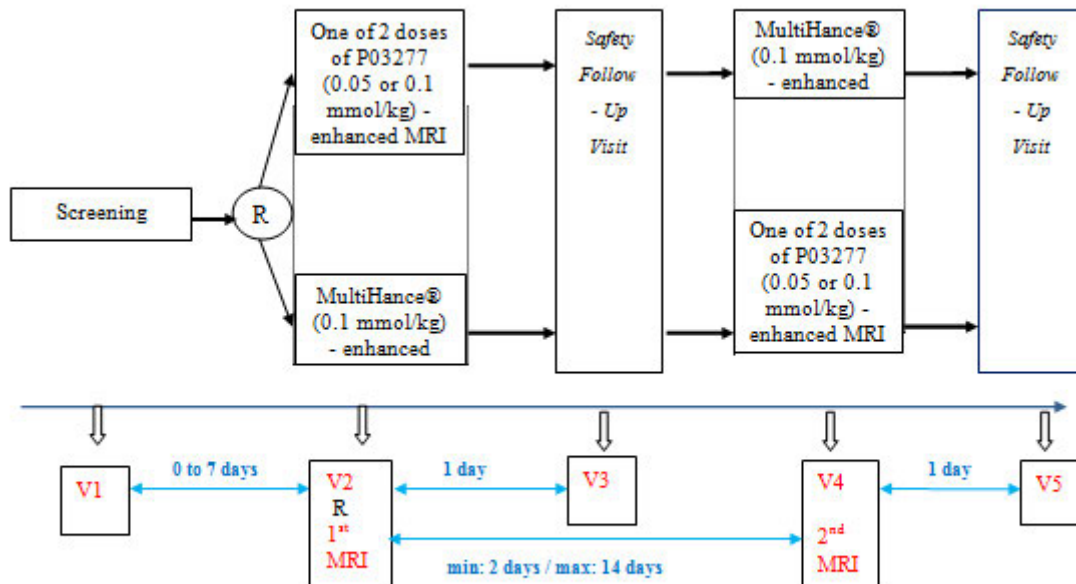
Descriptive statistics will summarize demographics, efficacy and safety data. Dose/response relationship of P03277 will be investigated for each IBR.

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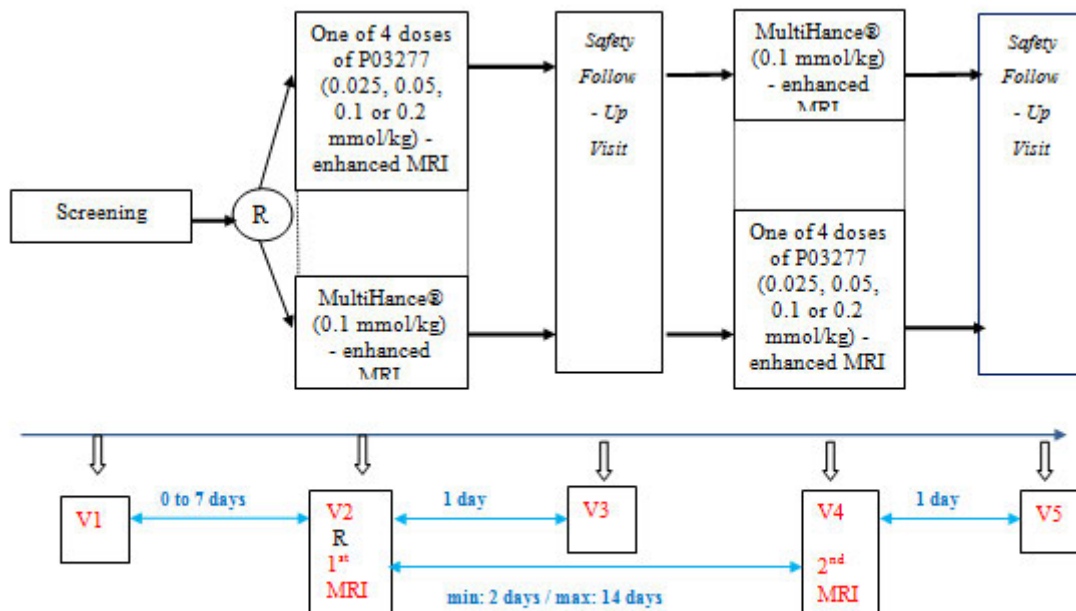
- (1) MRI procedures, at V2 and V4, should be performed on the same day of IWRS connection and contrast agent injection.
- (2) Urine or serum pregnancy test (if applicable) is to be done on site, and results must be available prior to IWRS connection and administration of P03277 and MultiHance®
- (3) eGFR is to be done locally, and results must be available prior to IWRS connection and administration of P03277 and MultiHance®
- (4) Clinical laboratory parameters will be analysed by the central laboratory: haematology and biochemistry, Cystatin C, see [Section 9.5.1](#) for details
- (5) Vital signs: BP=supine systolic and diastolic Blood Pressure, PR=Pulse Rate
- (6) 12-lead ECG to record heart rate, RR interval, PR interval, QRS duration, QT, QTc Bazett and QTc Fridericia. Starting at V2, Triplicate ECGs (3 measurements taken at approximately 1 min intervals) will be recorded prior each MRI and at each post-injection time point
- (7) Injection-site tolerance (burning, pain, eruption, extravasation, inflammation, or other) is to be assessed during the injection and at 45 ± 15 min and 2-4 hours post injection.
- (8) AEs will be assessed as soon as the subject's informed consent is signed and will end after the last follow up evaluation (1 day after last injection), unless the investigator becomes aware of a related, serious or not, adverse event after the last evaluation.
- (9) IWRS: connection should be done at each study visit and in case of screening failure or premature discontinuation
- (10) All the assessments performed prior to the first MRI at V2 will be considered as baseline value
- (11) 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.

Figure 1 : Study Diagram

First subset of subjects





Second subset of subjects

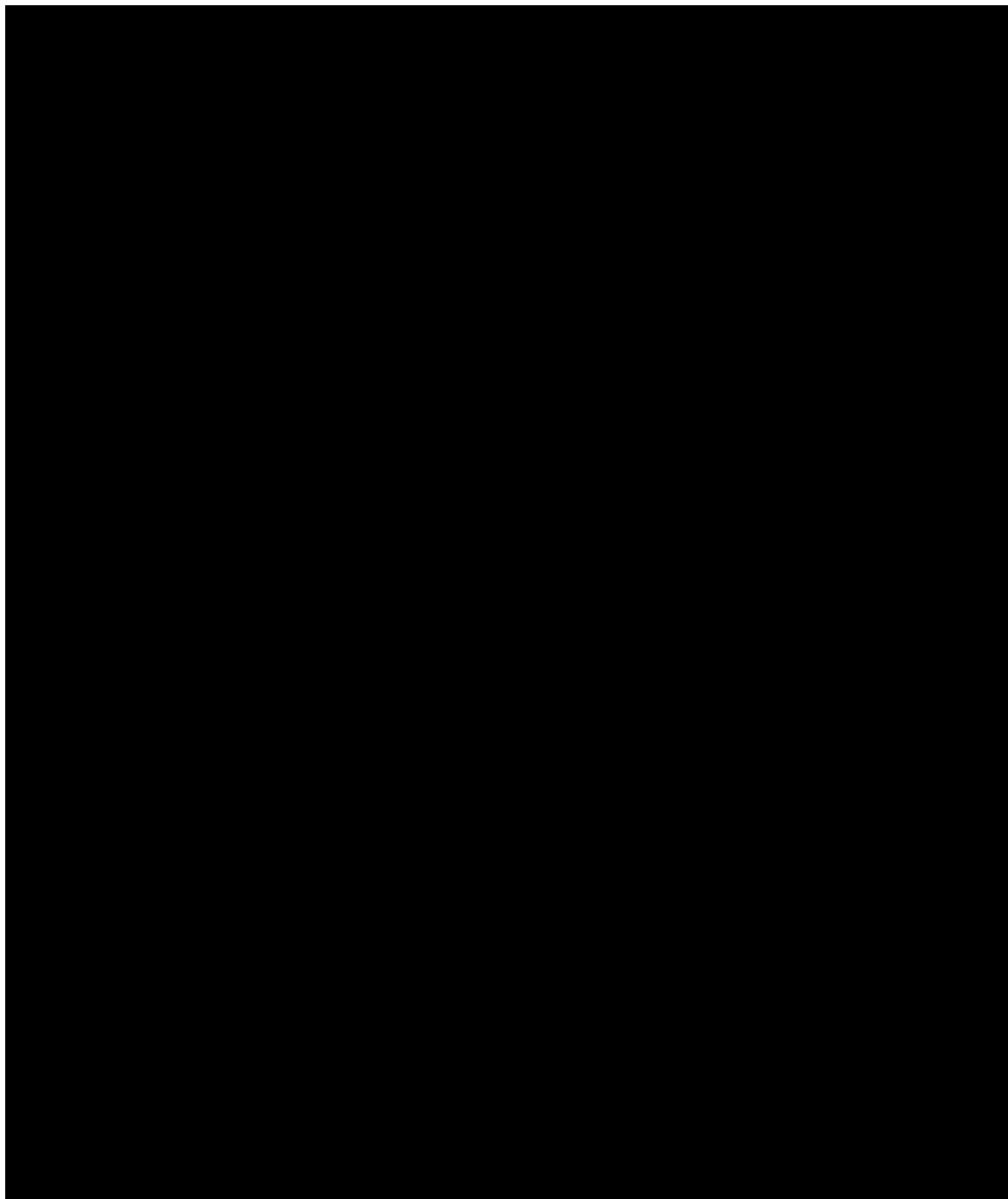


V: visit

R: Randomization via IWRS (to be done the same day as the 1st MRI)

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SIGNATURE PAGE



ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical classification system
BBB	Blood Brain Barrier
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BW	Body Weight
CA	Competent Authority
CNS	Central Nervous System
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
CNR	Contrast to Noise Ratio
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSE	Fast Spin Echo
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
IBR	Independent Blinded Reader

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
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean red blood Cells Volume
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
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
SPC/SmPC	Summary of Product Characteristics
Subject ID	Subject IDentification
SUSAR	Suspected Unexpected Serious Adverse Reaction
TE	Time of Echo
TI	Time of Inversion
TOI	Tissue Of Interest

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TSE Turbo Spin Echo
VAS Visual Analogic Scale
WBCs White Blood Cells




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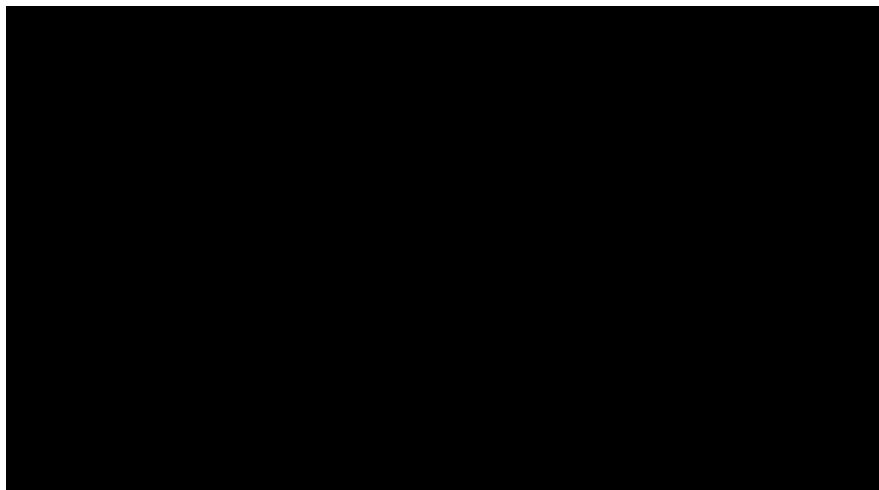
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P03277 is a Gd chelate with a very high stability, limiting the risk of release of toxic free Gd in the body. The results of preclinical data indicate a good tolerance and a low toxicity profile at dose levels and exposure much higher than the anticipated clinical dose. This satisfactory tolerance has been confirmed in a phase I study in a total of 54 healthy volunteers. No serious adverse events 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.

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).

The purpose of the study is mainly to determine the effective and safe clinical dose of P03277 injection to be recommended as the further P03277 approved dose for phase III studies, by comparing with approved GBCA for CNS indication (here MultiHance®, current commercial product with the highest relaxivity) using a cross-over design (allowing intra-subject comparison to evaluate the study primary criterion). This dose selection will be based on the superiority of P03277 in term of efficacy (based on CNR criterion) towards MultiHance® in subjects with CNS indication.

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2 STUDY OBJECTIVES

2.1 Primary Objective


To determine a safe and effective dose of P03277 based on a comparison of Contrast to Noise Ratio (CNR) between several doses, 0.025, 0.05, 0.1, 0.2 mmol/kg, of P03277 and MultiHance® at 0.1 mmol/kg.

2.2 Secondary Objectives

- To assess technical adequacy of images
- To evaluate capacity of lesion detection: number, size and location of lesions detected
- To evaluate diagnostic information using lesion visualization variables (lesion border delineation, internal morphology and degree of contrast enhancement)
- To evaluate diagnostic confidence
- To compare overall diagnostic preference between P03277 and MultiHance®
- To assess P03277 dose / response relationship for CNR and lesion visualization variables
- To evaluate the impact of P03277 and MultiHance®-enhanced MRI on subject treatment plan
- To assess the safety profile of P03277 as compared to MultiHance® after intravenous administration

2.3 Sub-Study / Ancillary Study Objectives

NA

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3 STUDY DESIGN

3.1 Protocol Description

The purpose of this phase IIb study is to determine an effective and safe clinical dose of P03277 injection for CNS lesion detection and visualization by conventional steady-state CNS imaging. Therefore, CNR, a well-known quantitative parameter directly related to contrast medium/GBCA efficacy, has been chosen as the primary endpoint in order to have a precise determination of P03277 clinical dose. Clinically meaningful parameter as lesion visualization which correlates with CNR will also be assessed, as a secondary primary endpoint.

This is a multi-center, international, prospective, double-blind, randomized, controlled, parallel dose groups, cross-over with comparator study in male and female subjects presenting with either known or highly suspected focal areas of disruption of the BBB (e.g. primary and secondary tumors, focal inflammatory disorders), who are scheduled to undergo a routine contrast-enhanced MRI of the CNS.

This study will be conducted in approximately 40 centers worldwide.

Two subsets of subjects (subset 1 and subset 2) will be included in the study. Subjects of the two subsets will be randomly assigned to one of the doses of P03277 and to one series of 2 MRIs performed each at two separate study visits (see [Figure 1](#)).


The first subset will consist of the first subject of each site. Indeed, in order to provide training images for the independent blinded off-site readers, to ensure that the imaging protocol/acquisition sequences has been appropriately programmed, and that the MR images produced can be transferred to the core laboratory, a dedicated subset of subjects (subset 1) will be enrolled for this purpose. Subjects of the subset 1 will be administered at 0.05 or 0.1 mmol/kg of P03277 with a 1:1: ratio and at 0.1 mmol/kg of MultiHance® and will perform all the study evaluations and safety assessments (see [Figure 1](#)). The two P03277 doses have been chosen as they are surrounding the potential targeted clinical dose. These subjects will not be considered for the efficacy analysis but only for the safety assessment. A maximum of forty (40) subjects (depending of the number of participating sites) will be included in the subset 1.

In addition of these subjects, two hundred and forty (240) subjects will be enrolled in a second subset (subset 2, see [Figure 1](#)). These subjects will be used for dose-finding part of the study in which the safety and diagnostic efficacy of P03277 will be evaluated in CNS MRI at doses of 0.025, 0.05, 0.1 and 0.2 mmol/kg (doses driven by efficacy in a safety acceptable range) with a 1:1:1:1: ratio versus MultiHance® (0.1 mmol/kg BW).

Subjects from both subsets will receive one of the doses of P03277 and one dose of MultiHance® by single IV injection at a rate of 2 mL/second followed by 0.9% saline flush in randomized order in two successive treatment periods separated by a wash out period of 2 days minimum up to 14 days.

During the course of the study, 2 MRIs will be obtained from each subject: one unenhanced and P03277-enhanced MRI; and one unenhanced and MultiHance®-enhanced MRI. MRI evaluations will be performed by on-site investigators and 3 independent off-site blinded readers.

To determine the exact matching of lesions throughout the different imaging sequences and MRI examination (P03277 and MultiHance®), an independent radiologist (lesion tracker) will perform 'lesion tracking' (except for the global matched pairs evaluation) based on the available CNS (brain/spinal cord) diagrams [REDACTED]

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The safety of subjects will be assessed using vital signs, 12-lead ECGs, injection site tolerance, clinical laboratory parameters (blood and urine) and by monitoring of adverse events (AEs). Safety assessments will be conducted over 1 day follow-up period after each MRI visit.

3.2 Study Duration

The study includes 5 visits: 1 screening visit, 2 MRI visits and 2 safety visits.

Subject eligibility will be determined at a screening visit performed up to 7 days prior to the first study MRI (the screening visit may occur the same day as visit 2 if all the inclusion/non-inclusion criteria are met).

Two MRI visits are to be performed, one session with P03277 administration and another session with MultiHance® administration. The interval between the 2 MR examinations is ≥ 2 days to avoid carryover effects but ≤ 14 days to minimize the risk of measurable disease progression or lesion evolution. Eligibility criteria will be checked prior to MRI procedures and confirmed via the IWRS to validate IMPs allocation.

Two safety visits will be performed during the study, one day after each MRI examination.

The minimum study duration per subject is 4 days and the maximum duration is 22 days.

The subject's participation is defined as the period from the screening visit (ICF signature) to the last study visit and defined in [Section 11](#) in case of premature discontinuation.

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


3.3 Interim analysis

No interim analysis is planned.

3.4 Study Committee

A Data Safety Monitoring Board (DSMB) will be set up for assessing the safety of the Investigational Medicinal Products (IMPs) during the study and for monitoring the overall conduct of the clinical trial (see [section 13](#)).

The investigators and Guerbet will be responsible to ensure the subjects stopping rules for safety reasons are applied (See [section 11.2](#)).

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4 SUBJECT SELECTION

The subject population is divided in 2 subsets of subjects (subset 1 and subset 2) who will have to meet all the study inclusion/non-inclusion criteria. In addition, subjects with brain metastasis will be randomized at a minimum of 20% of the subset 2 (stratification of 20% of subjects with brain metastasis per group of P03277 doses).


4.1 Inclusion Criteria

1. Female or male adult subject (subject having reached legal majority age).
2. Subject presenting, at the time of inclusion, with known or highly suspected focal areas of disrupted Blood Brain Barrier (BBB) (e.g., primary and secondary tumors, focal inflammatory disorders) including at least one expected enhancing lesion of minimum 5 mm (long axis). This lesion must have been detected on a previous imaging procedure (computerized Tomography (CT) or MRI).
3. Subject scheduled for a routine CNS contrast-enhanced MRI examination for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the study.
4. Subject able and willing to participate to the study.
5. 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.
6. Subject affiliated to national health insurance according to local regulatory requirements.

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

4.2 Non-Inclusion Criteria

1. Subject presenting with acute or chronic Grade III (at least) renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m² based on one eGFR assessment performed the day of the MRI prior to the first contrast agent injection.
2. Subject presenting with known class III/IV congestive heart failure according to the New York Heart Association classification (NYHA).
3. 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 and must be using a medically approved contraception method* until the last study visit).
4. Subject having received any investigational medicinal product within 30 days prior to study entry.
5. Subject previously enrolled in this study.
6. Subject presenting with any contraindication to MRI examinations.
7. Subject with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or other GBCAs.

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8. Subject having received any contrast agent (MRI or CT) within 3 days prior to study products administration, or scheduled to receive any contrast agent during the course of the study or within 24 hours after the second study product administration.
9. Subject having received any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc...) within 7 days prior to the first MRI or is expected/ scheduled to have a change in any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc...) in-between the 2 MRI examinations.
10. 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.
11. 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.
12. Subject related to the Investigator or any other study staff or relative directly involved in the study conduct.
13. Subject presenting with acute relapse of multiple sclerosis..

** 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).*


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

The diagnosis obtained from previous imaging examinations will be considered as medical history to assess inclusion criteria. All the study analysis will be based only on the images obtained through the study MRI.

4.3 Subject Identification

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

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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
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals

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.

Allocation of IMP to subject will be performed by an Interactive Web Response System (IWRS). The designated investigational staff will log into the system which will ensure that the appropriate IMP is allocated per subject.

5.1 Investigational Medicinal Product(s)

5.1.1. *Investigational Medicinal Product 1*

Name: P03277 XXXXXXXXXX

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: P03277 will be injected according to randomization at 1 of 4 different doses (1 dose per subject according to allocated randomized arm):


- First subset of subjects: 0.05 or 0.1 mmol/kg BW (corresponding to 0.1 or 0.2 mL/kg body weight) in a 1:1 ratio.
- Second subset of subjects: 0.025, 0.05, 0.1 or 0.2 mmol/kg body weight (corresponding to 0.05, 0.1, 0.2 or 0.4 mL/kg body weight) in a 1:1:1:1 ratio.

Sufficient IMP must be allocated to one subject by IWRS.

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

The P03277 administration is preferably performed by power injector in order to better control injection rate, but manual injection is also permitted in case it is necessary.

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

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5.1.2. *Investigational Medicinal Product 2*

Name: Gadobenate dimeglumine (529 mg / mL)

Brand name: MultiHance®

Pharmaceutical form: vial of 20 mL.

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

Concentration: 0.5 M

Dose per administration (as per Summary of Product Characteristics (SmPC)): 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg body weight.

The same dose of MultiHance®, 0.1 mmol/kg BW by single IV injection at a rate of 2 mL/second, will be injected to all subjects (subset 1 and 2)

Sufficient IMPs must be allocated to one subject by IWRS.

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

MultiHance® administration is preferably performed by power injector in order to better control injection rate, but manual injection is also permitted in case it is necessary.

Please refer to the local SmPC for more information on MultiHance®.

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 and MultiHance® will be performed by Guerbet (or its designee). The outer packaging will be the same for P03277 and MultiHance®, in order to ensure the double-blind conditions.


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 or one 20 mL vial of MultiHance®.

In case of damaged IMP, a new IMP will be allocated to the subject via the IWRS.

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.

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5.3 Condition of Investigational Medicinal Product allocation

5.3.1 Investigational Product(s) Allocation / Randomization

At visit 2, the subjects will be randomly assigned to one of the doses of P03277 and to one series of 2 MRIs performed each at two study visits separated by a wash out period of 2 days minimum up to 14 days. One series consists of the use of P03277 as contrast agent at visit 2 and MultiHance® at visit 4. The second series consists of the use of MultiHance® at visit 2 and P03277 at visit 4.

The P03277 dose to be injected to the subjects will be attributed by randomization (according to randomization list) at the time of visit 2 simultaneously with the MRIs order allocation.

The randomization scheme will allocate subjects to the two P03277 treatment arms (0.05 or 0.1 mmol/kg BW) in a 1:1 ratio for the first subset of subjects and to the four P03277 treatment arms (0.025, 0.05, 0.1 or 0.2 mmol/kg BW) in a 1:1:1:1 ratio for the second subset of subjects. The P03277 will be injected at a rate of 2 mL/second.

The same dose of MultiHance®, 0.1 mmol/kg BW by single IV injection at a rate of 2 mL/second, will be injected to all subjects.

The randomization will be done via IWRS with a stratification factor for the subset 2: presence of brain metastasis (yes/no) and performed in blocks to prevent unequal treatment allocation. For the subset 2, subjects with brain metastasis will be included at a minimum of 20% in each dose group of P03277.

The study design and the injection of the IMPs require identifying before the study start, two separate teams in each study site. One will manage the blinded data and another one will be unblinded and will be in charge of the IMPs preparation and administration. The unblinded staff will have to document in a separated subject's file all the unblinded information related to the IMPs and will have to complete a dedicated eCRF pages with restricted access.


During the course of the study, the two teams should not exchange any information regarding the subjects enrolled and the IMPs (nature, order of administration, dose). The subjects' files with unblinded data should not be filled with the subjects medical and study files in order to not break the blind. The unblinded documentation should be stored shielded from the view of the blinded staff. An initial shipment of IMPs will be sent to the investigational sites after having received regulatory authorization(s)/ethical approval(s) as per local requirements. Additional shipments will be sent according to subject recruitment progress of a given investigational site. The site should ensure to have enough IMPs before including a new subject. The site can log onto IWRS to know the IMPs stock status.

IMP receipt will be acknowledged by the investigator (or any designated person in his/her team) via IWRS.

Subject numbers will be sequential within each center.

At visit 2 and visit 4, once the eGFR and pregnancy test have been checked, the site should log onto the IWRS which will allocate IMP(s) number available at the site. This/these IMP(s) will correspond to the allocated treatment arm and to the contrast medium allocated for the enhanced MRI procedure.

In case one IMP breaks or becomes non-sterile or is not available, or any problem of IMP allocation (e.g. wrong IMP administered to the subject), the site must immediately report the incident into IWRS and to Guerbet's representative in order to ensure that all corrective actions are taken. Corrective actions may include transferring the IMP to quarantine to prevent further IMP allocation by the site until the

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situation is under control again. Detailed instructions can be found in the IWRS manual provided to the sites.

5.3.2 Double-Blind Conditions

In order to ensure the appropriate blinding of the study, several procedures will be put in place and are described below:

To ensure blinding of the investigator to the nature of the IMPs injected (P03277 or MultiHance®), a third party (site nurse, technician or physician) will be responsible for preparing and administrating the IMPs. This person ensures non-disclosure of information. He /she will stick the detachable label of the vial into the Subject's records or appropriate form. He /she will also write his/her name, date and signature and the subject number on the box, and after use, he/she will close the box with a seal.

The off-site blinded images evaluations will be performed by experienced radiologists who will not have been involved in the on-site clinical portion of the study. Image readings of all subjects will be evaluated in blinded conditions regarding the contrast agent injected, as described in [Section 9.4](#). The images used for blinded evaluation sessions must not contain any information regarding the subject's clinical data, study site, nature of IMP or the dose of P03277 ([section 9.4.6](#)). The steps for anonymizing images and transferring images to the Imaging Core Laboratory will be detailed in the "Site Imaging Manual".

Any disclosure relating to the nature of the contrast agent injected by the person responsible for IMP allocation will be considered a protocol violation.

5.3.3 Individual Study Treatment Unblinding

Unblinding of study product will be managed through the IWRS. In case of emergency, investigators will be allowed to request to the IWRS to unblind the study product allocated to a given subject under their responsibility. Study product should only be unblinded if absolutely necessary for the safety of the subjects and if unblinding impacts the management of medical cares (see [Section 10.4](#)).

Details concerning the decoding and the circumstances for breaking the code will be reviewed with the investigator and his/her team during the initiation visit.


The persons authorized to unblind study product during the study usually are: the principal investigator and the Sponsor Pharmacovigilance physician/officer.

If the Clinical Project Manager receives an external request for unblinding (Authorities, health care professionals taking care of the subject, etc.), he/she must inform the Sponsor Drug Safety Officer.

If the investigator and the Sponsor Pharmacovigilance physician/officer unblind the study product, he/she must inform the Clinical Project Manager as soon as possible by letter, fax or e-mail but shall not reveal the nature of the study product in order to protect as much as possible the double-blind design of the study.

Unblinding must be documented by indicating the subject number and demography characteristics (age, gender), the reason for unblinding, the date, time and identity of the person who performed the unblinding.

In case of unblinding, the subject will be withdrawn from the study.

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5.4 Investigational Medicinal Product Management

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense IMP(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, allows 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

An unblinded third party designated by the investigator will be in charge of product management and will keep accurate records of IMPs 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 managed by the unblinded staff (see [section 5.3.2](#)). When protocol required IMP administration conditions are not followed, reason(s) will be given and recorded by the third party.

These rules apply for both study subsets of subjects.

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6 CONCOMITANT TREATMENTS

Any treatment, including all medically approved contraception methods, homeopathic products, over-the-counter treatments, as well as prescription drugs, on-going at the time of subject's informed consent signed and/or any treatments administered during the study will be recorded in the medical file.

The following information must be provided:

- Drug (brand name or generic name)
- Route of administration
- Purpose (medical history/AE/ imaging pre-treatment/contraception/prophylaxis)
- Indication
- Duration of treatment

6.1 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 eCRF.

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.

In addition, no change should occur in any treatment or medical procedure (e.g., chemotherapy, radiotherapy, biopsy or surgery etc...) in-between the two MRIs.

6.2 Prohibited Concomitant Treatments

NA

7 EVALUATION CRITERIA

An overview of the efficacy variables, related to the second subset of subjects, is provided in the [Table 2](#) below. For the first subset of subjects, the same variables will be evaluated but only by the investigators and data will not be included in the efficacy analysis.

Table 2: Overview of Efficacy Variables

Variables	Combined unenhanced and P03277-enhanced MRI		Combined unenhanced and MultiHance®-enhanced MRI		Global matched Pairs read
	INV	IBR	INV	IBR	IBR
Primary efficacy variables:					
Signal intensity (lesion, healthy tissue and background)		✓		✓	
Secondary efficacy variables:					
Technical adequacy of images	✓	✓	✓	✓	
Number of lesions detected	✓	✓	✓	✓	
Size and location of lesions	✓	✓	✓	✓	
Border delineation	✓	✓	✓	✓	
Internal morphology	✓	✓	✓	✓	
Contrast enhancement	✓	✓	✓	✓	
Confidence in diagnosis	✓	✓	✓	✓	
Overall diagnostic preference					✓
Impact of P03277 and MultiHance®-enhanced MRI on subject treatment plan	✓		✓		

IBR = Independent Blinded Readers (off-site reads);

INV = Investigator (on-site read).

Following are the image sets that will be evaluated per subject:

Table 3: Images sets per subject

mage Set Number	Type
1a	Unenhanced MRI before P03277
1b	Unenhanced MRI before MultiHance®
2	P03277-enhanced MRI (GRE sequence for brain/SE sequence for spine)
3	MultiHance®-enhanced MRI (GRE sequence for brain/SE sequence for spine)
4	Global matched-pairs fashion (Combined unenhanced and P03277-enhanced MRI, Combined unenhanced and MultiHance®-enhanced MRI)

Combined set for P03277 is defined as unenhanced and P03277-enhanced MRI (set 1a and 2)

Combined set for MultiHance® is defined as unenhanced and MultiHance®-enhanced MRI (set 1b and 3)

7.1 Primary Criterion

The primary criterion (off-site read) is calculated by subject, and by independent blinded reader in a centralized procedure (off-site readers), in averaging the Contrast to Noise Ratio (CNR) for maximum 3 enhanced lesions. Only lesions detected by both MRIs after lesion tracking will be used. The evaluation will be done on combined images sets (1a, 2) and (1b, 3).

CNR is a variable derived for each lesion, from the Signal Intensity (SI) measurement. CNR will be calculated according to the following formula:

$$CNR = \frac{SI_{lesion} - SI_{ht}}{SD_{noise}}$$

where,


SI_{lesion} = the SI in the Region Of Interest (ROI) in the lesion

SI_{ht} = the SI in the ROI in healthy tissue (brain or spinal cord)

SD_{noise} = standard deviation of background noise.

The SI measurement will be performed by the independent blinded readers on the pre and post-injection, axial 3D T1 weighted Gradient Echo (GRE) for brain and sagittal T1-weighted Spin-Echo (SE) or Turbo Spin-Echo (TSE) for spine, sequences. The post CNR value will be normalized by the pre-CNR (baseline) value.

Measurements of the SI of the lesion are to be made on the best representative images of the pathology, along with the SI of normal brain (white or gray matter) or spinal cord tissue, and of the image background.

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These images will be selected according to the following:

- Up to 3 most representative lesions (largest enhancing lesion) will be measured separately.
- The lesion must have a size of at least 5 mm (long axis) to avoid partial volume averaging.
- The ROI for a lesion will encompass a homogeneous area within the lesion as large as possible.
- Normal tissue SI should be measured on the slice where lesion is present. For brain lesions, normal tissue ROI must always be drawn inside the brain, if possible, on the contra lateral hemisphere with respect to the identified lesions and regardless whether the lesions are intra- or extra parenchymal. Normal tissue ROI should be drawn in white matter if possible. For spine lesions, normal tissue ROI must always be drawn in adjacent portion of lesions in the spine, it can be done, if possible, in sagittal. For vertebral disease or disc disease, normal tissue ROI should be drawn in similar anatomy of non-involved level.
- Background measurement should be outside the brain but within the scan frame, phase shift noise should be avoided as much as possible.

7.2 Secondary Criteria

The following criteria will be evaluated either by the investigators (on-site read) or by the independent blinded readers (off-site read) or by both of them.

The evaluation will be done on image sets describe in [Table 3](#).

7.2.1 Technical adequacy of images (on-site and off-site reads)

Combined images sets (1a, 2) and (1b, 3) will be evaluated as adequate or not. Images are considered technically inadequate if artifacts completely compromise image interpretability. The reasons will be recorded:


- 1 = Artifacts due to subject
- 2 = Artifacts due to machine
- 3 = Artifacts due to contrast agent
- 4 = Injection technical failure
- 5 = Other, specify

7.2.2 Lesion detection capacity (on-site and off-site reads)

Number, size and location of lesions detected and the presence or absence of enhancement will be recorded.

For each combined image set (1a, 2) and (1b, 3), the investigator/independent blinded reader is to record the following:

- Number of lesions
- For the 3 most representative lesions, the following will be recorded for each lesion separately:
 - The largest diameter of the lesion
 - The location of the lesion

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- Presence or absence of enhancement (based on the evaluation ‘Degree of contrast enhancement (see 7.2.3))
- In case that more than 3 lesions are present, the investigator/independent blinded reader has to enter in the eCRF how many lesions are present (total number) and to specify the diameter of the smallest lesion.

7.2.3 Lesion visualization variables (on-site and off-site reads)

The investigator/ independent blinded reader will record each of lesion visualization variables (lesion border delineation, internal morphology and degree of contrast enhancement) for up to 3 most representative enhancing lesions, referring mainly to axial 3D T1-weighted GRE images for brain and sagittal T1-weighted SE/TSE images for spine, on a 4-point scale of the combined images sets (1a, 2) and (1b and 3).

○ Border delineation:

Delineation of the lesion border is defined as the distinction of lesion from surrounding tissues, structures, or edema; and the detection of extent of the lesion (for extra-axial lesions, this pertains to the definition of the space in which the lesion is present, and for intra-axial lesions, it pertains to the invasion of white matter, gray matter, or both; the neuroanatomical distribution of the lesion; and its mass effect). This criterion will be assessed through the following scale:

- 1 = none: no or unclear delineation
- 2 = moderate: some areas of clear delineation but also with some significant areas of non-distinct delineation
- 3 = good: almost clear but not complete delineation
- 4 = Excellent: border outline is sharp with clear and complete delineation

○ Internal morphology:

Internal morphology of the lesion includes an identification of lesion architecture and the intra-lesion features such as necrosis, hemorrhage and vascularity. This criterion will be assessed through the following scale:

- 1 = poor: poorly seen
- 2 = moderate: majority of lesion is poorly seen but with minor parts of lesion visible
- 3 = good: majority of lesion is clearly seen but with minor parts of lesion invisible
- 4 = excellent: lesion is well seen and can see “through” lesion to observe any complex areas of necrosis or hemorrhage or cyst formation.

○ Degree of contrast enhancement:

This criterion will be a qualitative assessment according to the following scale:

- 1 = no: no enhancement
- 2 = moderate: weakly enhanced
- 3 = good: clearly enhanced
- 4 = excellent: clearly and brightly enhanced

7.2.4 Diagnostic confidence (on-site and off-site reads)

The investigator/independent blinded reader will record in the eCRF his/her diagnosis and his/her confidence in diagnosis for each subject for each combined image set (1a, 2) and (1b, 3) according to [Table 4](#).

Table 4: Imaging diagnosis

Diagnosis	
Tumors	Primary Glial tumor, low grade (I/II) Glial tumor, high grade (III/IV) Glial tumor, tumor grade cannot be determined Meningioma Others, to be specified
	Secondary Brain metastasis
Inflammatory diseases	to be specified
Infectious diseases	Abscess Others, to be specified
Vascular diseases	Stroke Others, to be specified
Others	To be specified

Diagnostic confidence will be evaluated to determine the level of certainty that the investigator/independent blinded readers assign to a diagnosis. This is defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a subject.


The degree of confidence will be rated on a 5 point scale:

- 1 = nil: Very uncertain
- 2 = poor: Uncertain
- 3 = moderate: Moderately certain
- 4 = high: Good certainty
- 5 = excellent: Very certain

When the investigator/independent blinded reader chooses ‘not assessable’ for diagnosis, by definition the confidence level is 1 (= very uncertain).

7.2.5 Overall diagnostic preference (off-site read)

The evaluation will be performed in a global matched-pairs fashion (image set 4). For each randomized subject, all images (combined pre-injection and post-injection images) from the first MR examination, labeled as examination 1, will be displayed simultaneously with the corresponding images (combined pre-injection and post-injection images) from the second MR examination, labeled as examination 2.

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The assessment will be performed on all post-contrast T1-weighted images (i.e. axial 3D T1 weighted GRE for brain and sagittal T1-weighted SE/TSE for spine) with three-point scales:

- 1: for which examination 1 is preferred to examination 2
- 0: for which no preference is observed
- 2: for which examination 2 is preferred to examination 1

Readers need to select one or more of the following six reasons for this preference:

- Contrast enhancement was superior,
- Delineation of normal structure was better
- Delineation of at least one lesion was better
- Internal structure of lesions was better visualized
- More lesions were identified
- Diagnostic confidence was greater (specify one or more reason(s): detection of lesions, characterization of disease, assignment of a grade to disease (i.e., high or low grade in the case of intraaxial gliomas), definition of extent of disease, or other reasons that had to be specified on the eCRF)

7.2.6 P03277 dose / response relationship for CNR and lesion visualization variables

The relationship between dose and response will be evaluated graphically based on mean profile. Depending on the graphical results, a more complex model including study drug dose (as continuous variable) could be fitted to evaluate the relationship between dose and CNR increase.

7.2.7 Impact of IMPs-enhanced MRI on subject treatment plan (on-site read)

The impact on subject treatment plan will be assessed by on-site radiologists and will be summarized for each product group. At the end of visit 2 and at the end of visit 4, after having completed all the sequences of images required by the protocol (images sets 1a, 2 or sets 1b, 3), the investigator will have to document if the subject treatment plan could have been changed based on the images obtained (yes/no) and if yes, he/she would have to specify the therapeutic management proposed based on radiological assessment:


- Surgery
- Biopsy
- Chemotherapy
- Radiotherapy
- Other treatment: specify

7.2.8 Safety assessment

The safety assessments will be based on the following: Adverse Events (AEs), injection site tolerance, clinical laboratory parameters (blood and urine), vital signs and 12-lead ECGs. A central laboratory will be used to analyze and report blood chemistry/hematology/Cystatin C (eGFR would also have been evaluated locally prior to the MRIs). A central ECG vendor will be used to collect, assess and reports ECGs.

○ Adverse events

Adverse Event monitoring will be recorded throughout subject participation (see [section 3.2](#)).

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○ **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 injection (during the injection, 45 min \pm 15 min, 2-4 h post injection 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 from 0 (no pain) to 10 (maximal pain).

○ **Clinical laboratory parameters and urinalysis**

For each subject, central blood samples and urinalysis will be performed from visit 2 to visit 5. 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, glucose, Blood Urea Nitrogen (BUN) / urea, creatinine, eGFR, total protein, calcium, phosphorus, total bilirubin (and indirect bilirubin), conjugated bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Lactate DeHydrogenase (LDH), Triglycerides and Cystatin C.
- Urinalysis (dipstick): visual and chemical examinations (including color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin and urobilinogen).

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

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.

○ **Vital signs**


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

- Immediately prior to each contrast agent injection (baseline value)
- At 45 \pm 15 minutes and 2-4 hours following each contrast agent injection
- One day after each contrast 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.

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.

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○ **ECG monitoring**

The following parameters will be collected via an ECG device supplied by the ECG core laboratory: heart rate (RR interval), PR interval, QRS duration, QT, QTc Bazett, QTc Fridericia. The 12-lead ECGs will be measured prior to each contrast injection, and at 45 minutes \pm 15 minutes, at 2-4 hour, and 1 day after each contrast injection.

The ECG measured prior to the 1st contrast injection (at visit 2) will be considered as the baseline evaluation.


Triplicate ECGs (3 measurements taken at approximately 1 min intervals) will be recorded prior to each MRI and at each post-injection time point.

The subject is to be at rest for at least 5 minutes prior to any ECG recording.

All ECGs will be independently reviewed by a central reader (independent reviewer). Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

The investigator would have to give an overall interpretation of the ECG at each time point. All clinically significant abnormal changes will be recorded as AEs. Any clinically significant abnormal changes from baseline (Visit 2, prior to the MRI) must be followed until the abnormality is resolved or is adequately explained.

For ECGs a notable QTc change is defined as a QTc (Fridericia's or Bazett's) interval of greater than 450 ms for males and females. All such ECGs will be flagged by the core laboratory's cardiologist and require assessment for clinical relevance by the Investigator and if clinically significant to be reported as AEs.

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8 NUMBER OF SUBJECTS

Based on the hypothesis below, a total of 280 subjects will be enrolled in the study:


- First subset: maximum 40 subjects (depending of the number of participating sites) on the basis of 1 subject per site.
- Second subset: 240 subjects based on the following assumption: the study aims at detecting a minimum of 30% increase of CNR for at least one of the four tested dose of P03277 compared to control arm MultiHance® at dose of 0.1 mmol/kg BW. A sample size of 50 evaluable subjects per group is required to obtain a power of at least 90%, using a t-test of a normal mean difference with a 1-sided significance level of 0.025 (Holm's step-down method in a Multiple Comparisons Design) and a common standard deviation of 3.01. Therefore, a minimum of 50 evaluable subjects per dose group and a minimum of 200 evaluable subjects in total will have to be enrolled in this study.

An evaluable subject is defined as a randomized subject, 2 contrast agents administered, having undergone 2 complete, assessable and interpretable MRI examinations, presenting with at least one enhancing lesion of minimum 5 mm (long axis).

It is anticipated that some of the subjects will not complete both MRI evaluations. To offset this, an additional 10 subjects per group will be added to the 50 required leading to a total of 240 randomized subjects.

The number of non-evaluable subjects will be monitored to assess the necessity for a sample size increase. The decision to increase the sample size will be made by the sponsor when approximately 80% of the planned 240 randomized subjects are enrolled. The actual rate of drop-out subjects will be considered to assess the new number of subjects to be enrolled.

Subjects with brain metastasis will be randomized at a minimum of 20% of the second subset of subjects. Randomization will be stratified within brain metastasis (yes/no) in order to prevent unequal treatment allocation.

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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 [Section 14.3](#);
- The subject will be attributed a subject ID by eCRF;
- Verification of inclusion and non-inclusion criteria;
- Recording of demographic data (such as sex, ethnic data, date of birth (complete or partial as per local regulation)) measurement of height.
- 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 (name of contrast agent injected and tolerance will be recorded);
- Documentation of presence/absence of brain metastasis;
- Documentation of CNS disease justifying the MRI (e.g., brain metastasis of primary lung cancer);
- 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;
- A urine pregnancy test for all women of childbearing potential should be done and must be negative.
- IWRS connection for recording the subject screening visit;
- First study MRI visit and examination needs to be scheduled within 7 days (or the same day if all the inclusion/exclusion criteria are met).

9.1.2 Inclusion and imaging Visit – Visit 2 (Day 0) – First MRI examination

Procedures to be performed prior to MRI examination:

- Check of the eligibility criteria;
- Measurement of body weight;
- Any changes in concomitant treatments since the last visit will be documented;
- A urine or serum pregnancy test for female subject of childbearing potential will be performed prior to the study MRI 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);

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- Blood sample collection for serum creatinine dosage and verification of local estimated GFR value ≥ 60 mL/min/1.73 m² prior to the first MRI;
- Blood samples will be collected according to central laboratory manual;
- A urine dipstick will be done and results will be recorded on source documentation;
- Vital signs (systolic and diastolic Blood Pressure in supine position, Pulse Rate) and 12-lead ECGs (triplicate, 3 measurements taken at approximately 1 min intervals) will be recorded prior to contrast agent injection;
- Assessment of AEs will be documented;
- IWRS connection will be done to randomize the subject and to obtain the IMPs box number.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required pulse sequences specified in [Section 9.2.2](#).

The appropriate dose/volume of P03277 or MultiHance[®] (see [Appendices 19.1 and 19.2](#)) will be administered by IV as a bolus at the rate of 2 mL/second using ideally a power injector 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). P03277 or MultiHance[®] will be followed by a 0.9% saline flush using ideally a power injector.


The following information will be documented in the source document and reported on the restricted eCRF pages (unblinded staff access): the location of the IV injection line, the injection method (power injector or manual), actual volume injected and actual rate of the injection.

The start time of contrast injection and start time of post injection axial 3D T1 weighted GRE for brain and sagittal T1-weighted SE/TSE for spine, 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.

Procedures to be followed after MRI examination:

The subject will stay at the study site for at least 2-4 hours after the MRI examination is completed and the following procedures will be performed:

- Use/change of concomitant treatments during the visit;
- Vital signs (systolic and diastolic Blood Pressure and PR) and 12-lead ECG (triplicate ECGs, 3 measurements taken at approximately 1 min intervals) will be obtained 45 minutes \pm 15 minutes and between 2-4 hours after the injection of contrast agent. 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 , 45 minutes \pm 15 minutes and between 2-4 hours after the injection of contrast agent;
- Assessment of AEs will be documented;
- Evaluation of the potential impact of IMP-enhanced MRI on subject treatment plan;

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- Safety follow-up visit (Visit 3) needs to be scheduled 1 day post contrast agent injection;
- Scheduling of the second MRI examination (visit 4) between 2 days and 14 days post visit 2.

9.1.3 Safety Visit – Visit 3 (1 day post visit 2)

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

- Use/change of concomitant treatments will be documented;
- Blood samples will be collected according to central laboratory manual;
- A urine dipstick will be done and the results will be documented on the source documentation;
- Vital Signs (systolic and diastolic Blood Pressure in supine position, PR) and 12-lead ECG (triplicate ECGs, 3 measurements taken at approximately 1 min intervals) should be recorded;
- Injection-site tolerance is to be evaluated;
- Assessment of AEs will be documented;
- IWRS connection to record the study visit;
- Remind the date of visit 4 to the subject.

9.1.4 Imaging Visit - Visit 4 (from 2 days, up to 14 days post visit 2) – Second MRI examination


Procedures to be performed prior to MRI examination:

- Measurement of body weight;
- Any changes in concomitant treatments since the last visit will be documented;
- A urine or serum pregnancy test for female subject of childbearing potential will be performed prior to the study MRI; and must be negative;
- Blood sample collection for serum creatinine dosage and verification that the local eGFR value is ≥ 60 mL/min/1.73 m²;
- Blood samples will be collected according to central laboratory manual;
- A urine dipstick will be done and results will be recorded on source documentation;
- Vital Signs (systolic and diastolic Blood Pressure in supine position, PR) and 12-lead ECGs (triplicate, 3 measurements taken at approximately 1 min intervals) will be recorded prior to contrast agent injection;
- Assessment of AEs will be documented;
- IWRS connection will be done to obtain the IMPs box number;

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required pulse sequences specified in [Section 9.2.2](#).

The appropriate dose/volume of P03277 or MultiHance® (see [Appendices 19.1 and 19.2](#)) will be administered by IV as a bolus at the rate of 2 mL/second using ideally a power injector via a peripheral vein (the antecubital vein is preferred). The IV injection line will consist of a large bore indwelling

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catheter (at least 18 gauge). P03277 or MultiHance® injections will be followed by a 0.9% saline flush using ideally a power injector.

The following information will be documented in the source document and reported on the restricted eCRF pages (unblinded staff access): the location of the IV injection line, the injection method (power injector or manual), actual volume injected and actual rate of the injection.

The start time of contrast injection and start time of post injection axial 3D T1 weighted GRE for brain and sagittal T1-weighted SE/TSE for spine, 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.

Procedures to be followed after MRI examination:


The subject will stay at the study site for at least 2-4 hours after the MRI examination is completed and the following procedures will be performed:

- Use/change of concomitant treatments during the visit;
- Vital signs (systolic and diastolic Blood Pressure and PR) and 12-lead ECG (triplicate ECGs, 3 measurements taken at approximately 1 min intervals) will be obtained 45 minutes \pm 15 minutes and between 2-4 hours after the injection of contrast agent. 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, 45 minutes \pm 15 minutes, and between 2-4 hours after the injection of contrast agent;
- Assessment of AEs will be documented;
- Evaluation of the potential impact of IMP-enhanced MRI on subject treatment plan;
- Safety follow-up visit (Visit 5) needs to be scheduled 1 day post contrast agent injection.

9.1.5 Safety Visit – Visit 5 (1 day post visit 4)

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

- Use/change of concomitant treatments will be documented;
- Blood samples will be collected according to central laboratory manual;
- A urine dipstick will be done and the results will be documented on the source documentation;
- Vital Signs (systolic and diastolic Blood Pressure in supine position, PR) and 12-lead ECG (triplicate ECGs, 3 measurements taken at approximately 1 min intervals)) should be recorded;
- Injection-site tolerance is to be evaluated;
- Assessment of AEs will be documented;
- IWRS connection to record the subject end of study.

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The schedule of time and events to be performed is given in [Table 1](#) (study flow chart).

During the course of the study, if a subject is screen failed or is prematurely discontinued, the new subject status should be recorded in the IWRS and in the eCRF.

9.2 Imaging Protocol

9.2.1 MR equipment

The procedure will be performed using a MRI scanner that can perform the required pulse sequences with a dedicated head coil or a spine coil. MRI units with 1.5T or 3T magnetic field will be used, regardless of the manufacturer. The following information must be recorded: the manufacturer, model, software version, and field strength of the MRI device.

For a single subject, it is mandatory to use the same MR equipment for the two MRI examinations required by the protocol.

9.2.2 MRI sequences

The same parameter setting must be used for unenhanced images and for contrast-enhanced images in each subject (i.e., axial 3D T1 weighted GRE for brain and sagittal T1-weighted SE/TSE for spine).

The required sequences and parameters for P03277 and MultiHance[®] per subject should be identical as follows:


For brain (axial orientation and whole brain are required):

- Unenhanced :
 - 3D T1-weighted GRE images
 - 2D T2-FLAIR
 - T2-weighted TSE images
- Contrast-enhanced:
 - 2D T1-weighted SE/TSE images
 - 3D T1-weighted GRE images (sequence parameters and slice positioning should be identical to pre-contrast 3D T1-weighted GRE)

The 3D sequence has the advantage of enabling multiplanar reformatted images to different orientations. 3D-GRE provided significantly better images than the SE sequence in terms of the border and delineation of lesions and overall image quality. In addition, the 3D-GRE sequence is supposed to show fewer pulsation artifacts. 3D-GRE is more sensitive sequence for detecting small lesions.

For spine:

- Unenhanced :
 - T2-weighted TSE images (sagittal)
 - T1-weighted SE/TSE images (sagittal)
- Contrast-enhanced :
 - T1-weighted SE/TSE (axial)
 - T1-weighted SE/TSE (sagittal)

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It is not allowed to add any sequence, other than the one described above, between contrast agent injection and axial 3D T1-weighted GRE for brain and sagittal T1-weighted SE/TSE for spine.

Deviations from the specified MRI procedure will be recorded in the CRF.

Sequence parameters for brain and spine imaging will be provided in the site imaging manual.

9.3 On Site Reading of Images

For each investigational site, one experienced neuroradiologist or radiologist experienced in neuro-imaging will be appointed at the start of the study to read all images of subjects included at the site. As far as possible, a second (neuro)radiologist should be identified in each site and trained to the protocol in case the first (neuro)radiologist is not available to read the images.

9.4 Off Site Reading of Images

Images will be evaluated by prospective evaluation of the blinded images in a centralized manner. All images will be sent to a core laboratory, which will prepare the images for evaluation. The file headers of all the images transmitted in DICOM format are to be edited to remove subject or center identification. For all images, any sequence information will be removed. Scalar information in the MR images will be preserved. A complete audit trail of any changes to the file headers will be maintained.

The blinded image evaluations will be performed by 3 independent blinded radiologists. An eCRF will be used to ensure that the images and the diagnostic findings are properly aligned and to ensure that all data necessary for the study purpose are documented by the independent blinded readers.

9.4.1 Manuals and Supplies

Guerbet (or the imaging core laboratory) will document the imaging tasks and obligations of the investigational site in a site imaging manual. As defined in [Section 9.2](#), the standardized image acquisition guidelines or imaging protocol 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 the imaging core laboratory.

Guerbet (or its imaging core laboratory) will document the central imaging process in a blinded image evaluation charter.

9.4.2 Site Qualification

Guerbet's designee (imaging core laboratory) will perform pre-study site selection and site training. These contacts will ensure that the protocol-stipulated imaging can be performed by the site, might be programmed and prepared prior to enrollment of the first subject and that the site imaging manual will be accurately followed by the investigator.

The images collected from the first subject (subset 1) of each site will be used by the imaging core laboratory to confirm to the sites that they are in accordance with the study imaging protocol requirements (see [section 9.4.4](#)). Guerbet or its designee (imaging core laboratory) should confirm first to the investigator that the site is qualified before continuing subject's enrolment.

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9.4.3 Receipt and Tracking of Images

Guerbet (or imaging core laboratory) will request that investigational sites submit anonymous images to the imaging core laboratory in a format that will be agreed prior to study start. Images will be tracked in the database of the imaging core laboratory.

9.4.4 Image Processing and Quality Check

Images received by the imaging core laboratory as digital data will be translated from proprietary formats to a standard format. This data translation step enables capturing direct digital data. Subject identifiers are confirmed as removed, and the original digital data from the site is archived and stored.

The imaging core laboratory will ensure that all imaging protocol requirements have been followed. In the event that a problem with an image is identified (e.g.: inappropriate anatomical coverage, inconsistency of image parameters with the imaging protocol, poor quality images), the investigational site will be notified on the nature of the problems and the steps required for corrective action. The Imaging Core Laboratory will follow-up on all cases requiring remedial action by the investigational sites. Guerbet (or the Imaging Core Laboratory) may conduct site re-training for investigator sites with recurring image quality issues.

9.4.5 Independent Blinded Readers Training

All independent off-site readers will be trained to the study reading specifications. Before the readers start the readings, they will have to successfully complete a serial of training sessions (refer to “blinded image evaluation charter” for details).

Each reader will need to acquire an adequate understanding of definition of terms to be used in image evaluation and classification. To sufficiently understand different point scales used to evaluate lesions by reviewing training cases in order to reach an acceptable intra-reader and inter-reader variability.


The images collected from the subjects of the subset 1 as well as images from other studies will be used to conduct the training of the independent blinded readers (off-site).

The independent blinded readers (off-site) will not been trained on the study inclusion/non-inclusion criteria. Details on the protocol and anatomic orientation to the images will not be provided to the independent blinded readers.

9.4.6 Image Randomization

Blinded image evaluations will be conducted per batch such that each blinded image evaluation session will contain an appropriate number of cases to enable completion by a reader. The subjects within each batch will be ordered at random without stratification into groups of subjects (when applicable). Various modalities of images from the same subject will not be presented in the same batch and the imaging core laboratory will ensure an appropriate wash-out period between the evaluations of images from two modalities for the same subject, to minimize recall bias. Each images set will be assigned 1 randomization number. The randomization lists for all 3 blinded image evaluation sessions will be created by the core laboratory. The randomization codes will be kept during the study by the imaging core laboratory. The access to the randomization codes will be strictly limited. Randomization codes will be transferred to Guerbet after database lock.

The blinded image evaluations will be performed in parallel to the ongoing recruitment in the clinical trial. For the first 4 image sets (see [Table 3](#)), the image material will be ordered according to the sorted order of the randomization lists that are prepared prior to the blinded reading.

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9.4.7 *Blinded Assessment of Images*

Imaging database including all evaluable MR images will be assessed by three independent, board-certified and fully blinded readers, with expertise in the interpretation of MRI of the CNS diseases, who will not participate in the study, and do not have affiliation with any institution where the study will be conducted.

The term “independent” means that the readers involved in centralized review do not participate in image acquisition and images are read outside the image acquisition site.

The term “fully blinded” means that the readers will not have any knowledge of (i.e., will be blinded to) the following information:

- Subject-specific information (including name, identifiers, medical history, clinical examination, and laboratory results)
- Institution name
- Subject enrolment information (including inclusion and non-inclusion criteria)
- Results of any imaging examination other than the imaging examination to be read
- Findings of any other readers (e.g., investigators, on-site readers and other central readers)
- Data related to contrast medium nature and dosage
- Type of MRI and image sequence other than information apparent from the aspect of the images themselves
- Final diagnosis and subject outcome

No communication on subject specific image findings will be allowed between the 3 independent blinded readers once the blinded reviews begin.


To ensure that the centralized reading evaluations remain independent, each individual reader evaluation will be locked as they occur (i.e., it will not be possible to alter the evaluation).

9.4.8 *Inter & Intra-Reader Variability Assessment*


The assessments of inter- and intra-reader variability will be done in the final analysis.

- **Inter-reader variability** will be evaluated on the whole set of study subjects, since each case will be read by 3 different readers.
- **Intra-reader variability**: individual readers will perform repeat image evaluations of 10% of cases randomly determined. The cases used for intra-reader variability assessment will be re-introduced randomly and re-read during the course of the reading. To minimize recall bias, intra-reader variability will be assessed approximately after the first 30 cases are reviewed and no sooner than two weeks from the original reviews of these subjects. Results of the original reviews for these cases will not be available to the reader. Only the first evaluation of a given image set will be included in the efficacy analysis.

9.4.9 *Lesion tracking (not applicable for global matched-pairs reads)*

All 3 blinded readers will independently identify the location of all the lesion(s) detected in the image sets. The location for each lesion will be marked along with a number in ascending order on a CNS diagram 

To allow exact matching of lesions throughout the different imaging sequences examinations, an independent radiologist (lesion tracker) will perform the ‘lesion tracking’ based only on the available CNS diagrams for a given subject. All CNS diagrams for each subject will be displayed simultaneously.

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Because a unique numbering of the lesions cannot be ensured during the blinded image evaluations by 3 readers, the lesion tracker will assign a new number for each lesion to be tracked, which will then be matched and correlated to the numbers indicated on the CNS diagrams.

The independent lesion tracker will not obtain any information about the contrast medium used for the enhanced MRI.

9.4.10 Image Warehouse and Final Deliverables

All imaging data will be maintained in a secure environment. The imaging core laboratory 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 so that these data may be audited if necessary. The resulting database will be transferred to Guerbet after database lock for archiving.

The CDs/DVDs produced to record the ROIs (for off-site read only) are to be used for SI measurements and will be given to Guerbet at the end of the study once the off-site readers would have completed all the images reads.

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 and centrally. 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.

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.

9.5.2 Centralized assessment of ECG

The 12-lead ECGs will be sent to the ECG core laboratory continuously during the course of the study for evaluation by an independent cardiologist. The following parameters will be evaluated for individual subjects and time points:

- RR interval and heart rate
- Intervals: PR, QRS, QT [plus calculated QTc (Fridericia and Bazett methods)]
- ST segments, T-wave morphology, U-wave
- Global morphology


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The QTc is the heart rate corrected QT interval (calculation according to Fridericia and Bazett method).

The ECG core laboratory will record whether the cardiologist is unable to evaluate the ECG. A comment field will be provided for the cardiologist to indicate factors that effected the interpretation; e.g. lead reversal.

All ECGs changes considered as abnormal and clinically significant will be reported as AEs.

For ECGs a notable QTc change is defined as a QTc (Fridericia's or Bazett's) interval of greater than 450 ms for males and females – all such ECGs will be flagged by the core laboratory's cardiologist and require assessment for clinical relevance by the Investigator.

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

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related 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 experienced abnormality 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 eCRF and monitored from onset to resolution or stabilization of sequelae. If no follow-up is performed, the investigator must provide a justification in the medical file.

In order to ensure complete safety data collection, all Adverse Events occurring during the time of the subject's participation in the study, must be reported and monitored even if no IMP was administered. The investigator shall document all Adverse Events in the medical file and the appropriate section of the eCRF.

As a reminder the subject's participation is defined as the period from the screening visit (ICF signature) to the last study visit and defined in [Section 11](#) in case of premature discontinuation.

Safety information is to be collected by the investigator with the same procedure as Adverse Events: treatment 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, 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).


As an exception, as the study aims to assess the effective dose of P03277, doses with lesser efficacy are expected and will be considered while analyzing the primary endpoint.

In this protocol, the overdose is defined as more than 0.3 mmol/kg for P03277 and more than 0.2 mmol/kg for MultiHance®. 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 eCRF.

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- **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 – apart from imaging procedure:**
 - 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 :
 - Study treatment unblinding
 - IMP definitively stopped: IMP was permanently discontinued.
- **Other action taken:**
 - AE-targeted treatment: the subject took a treatment (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the eCRF ("concomitant drug" section)
 - Other AE-targeted action: subject used other therapeutic measures (e.g. ice, heating pad, brace, cast...) or subject underwent a procedure (physiotherapy,

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additional laboratory test...) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the eCRF.

- **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 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 related 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.

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

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

- Any hospitalization that had been planned before the study and that will take place during the study, 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 checkup).

10.2.2 Procedure for Reporting Serious Adverse Events

SAEs occurring from ICF signature until completion of the study for each subject are to be reported to Guerbet Pharmacovigilance department.

The investigator **must immediately and within 24 hours** 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 Guerbet 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 (subject ID) 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 eCRF as requested in [Section 10.1.2](#)

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

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

In addition, if occurring after the end of the subject's follow-up period defined for this study (i.e. within 1 day post second IMP administration), serious adverse and/or unexpected events that the Investigator thinks may be associated with the study treatment/procedure must be reported to Guerbet regardless of the time between the event and the end of the study.

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 Guerbet 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 AEs, the special situations described below should be handled with the same procedure as the SAE reporting procedure.

10.3.1 Pregnancy

Any pregnancy (with or without an AE 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 visit 4 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 to the investigational sites. 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).

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.

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10.4 Unblinding Procedures

The investigator may, under exceptional circumstances unblind the individual study treatment group if he/she considers that this procedure is relevant to the safety of the study subject. Individual study treatment unblinding is described in [Section 5.3.3](#). Unblinding must be documented in the subject medical file, completed in the SAE form sent to Guerbet Pharmacovigilance department, if applicable.

Suspected Unexpected Serious Adverse Reaction (SUSARs) will be unblinded by Guerbet Pharmacovigilance Department for regulatory reporting purposes; however, these SUSARs will remain blinded to the investigator and to Guerbet personnel responsible for study management, data analysis, and interpretation of results at the study's conclusion.

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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, if applicable 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 Visit 2 (first contrast agent injection and MRI procedures) will be considered screening failures.

If a subject discontinues before Visit 2, the IWRS must be notified and only the reason for being screening failure will be documented on the source document and in the eCRF (see [section 15.3.2](#))

Criteria for premature discontinuation of subjects:


- 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 eCRF). 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, biopsy or surgery etc...) between the two MRIs;
- At the discretion of the investigator if, for example, the subject safety or well-being is not compatible with study continuation;

Specific subjects study stopping rules:

If any of the events described below occur, injection of IMPs should not be done and the subject should be discontinued from the study:

- Renal toxicity characterized by an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 µmol/l) and/or an increase in serum cystatin C by more than 25% compared to the baseline value
- QTc Bazett or QTc Fridericia >500 ms or an increase of > 60 ms over baseline
- Any events which investigator or Guerbet considers raising a significant concern

The data to be reported in the eCRF for subjects subsequently discontinuing from the study are detailed in the protocol [section 15.3.2](#).

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For subjects withdrawn from the study, all data available at the time of withdrawal will be reported in the medical file and the eCRF (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., AEs and injection-site tolerance, as appropriate), unless the subject withdraws consent for further data collection/participation for/in the study.

Enrollment of additional subjects:

There is no replacement scheduled for subjects withdrawn prematurely. However, if the number of subject prematurely withdrawn is higher than expected the sample size will be increased to ensure a number of evaluable subjects equal to 50 for each study group.

Management care of discontinued subject:

In the event of premature discontinuation, subjects will receive adequate follow-up from on-site investigators; other diagnostic products available will be introduced if necessary.

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12 STATISTICAL ANALYSIS

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

12.1 Subjects Included in the Analysis

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

The Extended 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 contrast agent, regardless of the quantity. Subjects of subset 1 will be included in this set. This set will be used for evaluation of safety.

The Full Analysis Set will include all subjects, except subjects from subset 1, who have valid assessments of the primary criterion. This set will be used for description of demographic data, baseline characteristics data, medical history, concomitant treatment and 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. This set will be used for the evaluation of the primary efficacy criterion.

If the PP set differs from the FAS by more than 15%, description of demographic data, medical history, concomitant treatment and evaluation of efficacy will be repeated for this set.

12.2 Demographic and Baseline Data

Demographic parameters are age, gender, ethnic origin, childbearing potential, body weight, height, and body mass index (BMI). Baseline characteristics are the subject's history (including the medical history, the clinical indication for MRI and the presence or absence of brain metastasis) and the concomitant treatments.


Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height and BMI. Frequency and percentages will be calculated for gender, subjects' history characteristics and concomitant treatments.

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

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

12.3 Efficacy Data/ Dose selection

In this section, treatment groups refer to doses of P03277 (0.025, 0.05, 0.1 and 0.2) and matching MultiHance® administration (i.e. P03277 0.025 mmol/kg versus matching dose of MultiHance® 0.1 mmol/kg; P03277 0.05 mmol/kg versus matching dose of MultiHance® 0.1 mmol/kg; P03277 0.1

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mmol/kg versus matching dose of MultiHance® 0.1 mmol/kg and P03277 0.2 mmol/kg versus matching dose of MultiHance® 0.1 mmol/kg)

Primary analysis of the primary criterion

The primary objective of the study is to determine a safe and effective dose of P03277 based on a comparison of Contrast to Noise Ratio (CNR) between several doses, 0.025, 0.05, 0.1, 0.2 mmol/kg, of P03277 and MultiHance® at 0.1 mmol/kg.

The primary criterion is the Contrast to Noise Ratio (CNR) calculated from the Signal Intensity (SI) measurement of maximum 3 enhanced lesions by the 3 independent blinded readers (see [section 7.1](#))

The primary analysis will test differences of means of primary criterion for each dose of P03277 compared to MultiHance® and will be done for each of the 3 independent blinded readers (off-site) using the PPS. Holm's step-down method will be used to address multiplicity testing considering the 4 treatment groups to be tested.

Statistical hypothesis for the primary analysis:

For each reader and each treatment group, a covariance analysis for correlated data will be done for assessing the primary criterion. Factors include in the model are treatment (P03277 and MultiHance®) and the pre CNR measurement for unenhanced lesions (baseline).

Differences between means will be tested for each treatment group using Student's t-test according to the following items:

- μ_i is the expected average of CNR of enhanced lesions for each dose of P03277 (where i is corresponding to one dose of P03277)
- μ_0 is the expected average of CNR of enhanced lesions for corresponding MultiHance® dose

Null hypothesis

$H_i: \mu_i - \mu_0 \leq 0, i = 1 \dots 4$

Alternative hypothesis


$K_i: \mu_i - \mu_0 > 0, i = 1 \dots 4$

For each treatment group, the p-value for comparing the doses of P03277 with corresponding MultiHance® is calculated for testing above hypotheses.

Holm's step-down method:

Let p_1, p_2, p_3, p_4 be the ordered p-values (from the lower to the upper value) and H_1, H_2, H_3, H_4 be the corresponding ordered null hypothesis. The testing procedure starts with the most significant comparison and continues as long as tests are significant (meaning that the alternative statistics is met). The procedure stops the first time a non-significant comparison occurs and all remaining hypotheses will be not tested.

In the first step, H_1 is rejected if $p_1 \leq \alpha/4$, in the second step (if any) H_2 is rejected if $p_2 \leq \alpha/3$, in the third step (if any), H_3 is rejected if $p_3 \leq \alpha/2$ and in the fourth and last step, H_4 is rejected if $p_4 \leq \alpha$, with α being the 1-sided significance level of 0.025.

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Selection basis for clinical dose:

The effective clinical P03277 doses will be the doses for which at least 2 out of the 3 off-site blinded readers meet the alternative hypothesis for the primary endpoint.

If more than one effective clinical dose is identified based on the primary statistical analysis described above, then the clinical target dose will be selected according to the clinical benefice/risk ratio for each of them including the efficacy secondary criteria analyzed in this study.


Secondary analyses of the primary criterion

- **FAS analysis**
 - The primary analysis will be repeated using the FAS.
- **Overall analysis**
 - The primary analysis will be repeated by pooling together all off-site readers using the FAS and the PPS.
- **Centre Effect**
 - By-site summaries will be produced to look for potential disparities among the sites (center effect) using the FAS and the PPS. The p-values will not be reported for the by-site summaries.
- **Dose/response evaluation**
 - The relationship between doses of P03277 and response will be evaluated graphically based on mean profile during the study using the FAS and the PPS.
 - Depending on the graphical results, a more complex model including doses of P03277 (as continuous variable) could be fitted to evaluate the relationship between doses and CNR increase.

Analyses of the secondary criteria

All analyses of the secondary criteria (based on combined unenhanced/enhanced contrast images) will be done using the FAS except otherwise specified.

- **Technical adequacy of images**
 - The adequacy of images will be assessed by off-site readers and on-site radiologists as adequate, yes or no and reason for inadequacy will be recorded using a 5-items list. Adequacy of images will be tabulated for each dose of P03277 by treatment groups; off-site and on-site reader's outcomes will be separately analyzed.

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○ **Lesion visualization variables**

- Off-site blinded readers and on-site radiologists will grade the lesion visualization of the three largest representative lesions, using 3 variables (lesion border delineation, internal morphology and degree of contrast enhancement) assessed on a 4-point scale ranging from 1 to 4.

For each variable, one subject score will be computed in adding up all lesion scores within subject by treatment groups.

Subject score will be tabulated for each dose of P03277 by treatment groups; each off-site and on-site reader's outcomes will be separately analyzed.

- Dose/response evaluation as per primary endpoint will be performed also for the subject score of each lesion visualization variable by each off-site reader.

○ **Lesion detection capacity**

- The number of lesions by subject will be assessed by off-site readers and on-site radiologists for each dose of P03277 by treatment groups. Number of lesions will be tabulated for each dose of P03277 by treatment groups; off-site and on-site reader's outcomes will be separately analyzed.
- The size of the three largest representative lesions by subject will be assessed by off-site readers and on-site radiologists for each dose of P03277 by treatment groups. Size of lesion will be summarized for each dose of P03277 by treatment groups; off-site and on-site reader's outcomes will be separately analyzed.
- The localization of the three largest representative lesions by subject will be assessed by off-site readers and on-site radiologists for each dose of P03277 by treatment groups. Localization of lesion will be displayed for each dose of P03277 by treatment groups; off-site and on-site reader's outcomes will be separately analyzed.
- The presence or absence of contrast enhancement for the three largest representative lesions will be assessed by off-site readers and on-site radiologists for each dose of P03277 by treatment groups. Contrast enhancement of lesion will be displayed for each dose of P03277 by treatment groups; each off-site and on-site reader's outcomes will be separately analyzed.

○ **Diagnostic confidence**

- The diagnosis of each lesion according to off-site readers and on-site radiologists when evaluating each dose of P03277 by treatment groups will be displayed; off-site and on-site reader's outcomes will be separately analyzed.
- The level of diagnostic confidence of off-site readers and on-site radiologists when evaluating each dose of P03277 by treatment groups will be graded using a 5-point scale with the following points: nil, poor, moderate, high and excellent. Diagnostic confidence will be tabulated for each dose of P03277 by treatment groups; off-site and on-site reader's outcomes will be separately analyzed.

○ **Overall diagnostic preference**

- The level of overall diagnostic preference of images of off-site readers when evaluating in global matched-pairs fashion all post contrast T1-weighted images (i.e. axial 3D T1

weighted GRE for brain and sagittal T1-weighted SE/TSE for spine of blinded images MRI 1 versus MR2) for each dose of P03277 will be evaluated according to their preference: for the overall diagnostic, MRI 1 is preferred to MRI 2, no difference between the 2 MRIs or MRI 2 is preferred to MRI 1.

For the analysis, the results will be displayed as follows:

- P03277 is preferred to MultiHance®
- No difference between the 2 treatments
- MultiHance® is preferred to P03277

Diagnostic preference of images will be tabulated for each dose of P03277.

- The reason of this preference will be displayed.
- **Impact of contrast agent-enhanced MRI on subject treatment plan:**
 - The impact on subject treatment plan will be assessed by on-site radiologists and will be summarized for each dose of P03277 by treatment groups.

12.4 Safety Data

Safety analysis will be done using the safety set.

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 (and not on the number of AEs) except otherwise specified.


Adverse event 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 (see [Table 5](#) below):

Table 5: Time period for the assessment of AEs

		Start	End
Period 1	Before treatment	<i>Informed consent signature</i>	<i>Start of study treatment of the first MRI</i>
Period 2	Period of first MRI	<i>Start of study treatment of the first MRI</i>	<i>Start of study treatment of the second MRI</i>
Period 3	Period of second MRI	<i>Start of study treatment of the second MRI</i>	<i>End of study</i>

Events will be classified by period according to time of onset.

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Events will be classified as treatment-emergent if they started or increased in severity during period 2 or period 3. This will also include events with missing intensity if the end time is after induction or missing.

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 the combined periods 2 and 3 and for each period separately for:

- At least one TEAE
- At least one adverse reaction (relationship to study treatment classified as ‘Related’)
- At least one TEAE with each of the following classifications of action taken with study treatment:
 - Dose not changed
 - IMP withdrawn
- At least one TEAE with each of the following classifications of outcome:
 - Recovered/resolved
 - Recovered/resolved with sequelae
 - Not recovered/Not resolved
 - Fatal

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 (periods 1 to 3 combined).

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) for the combined periods 2 and 3 and for each period separately. 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)

Summaries by SOC and PT will be presented for treatment-emergent events for the combined periods 2 to 3 and for each period separately for:

- At least one TEAE
- At least one of the most common TEAEs (PT occurring in at least 10% of subjects on P03277 0.2 mg)
- At least one TEAE by most severe intensity (i.e. classified as ‘severe’)

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

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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 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 7.2.8](#)) and according to their clinical significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

ECG


ECG data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of ECG data to their normal ranges and according to their clinical significant changes. Notable QTc value will be presented for raw data and changes (see [section 7.2.8](#)). Quantitative analyses will be done by tabulating raw data and change from baseline.

12.5 Handling of Missing Data

No imputation will be performed in this study.

12.6 Interim Analysis

Not applicable.

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13 STUDY COMMITTEE

The purpose of this phase IIb study is primarily to determine an effective and safe dose of P03277 injection, by comparing with GBCA approved for CNS indication.

The IMPs used, in this study, as contrast agents belong 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.


The study duration per subject is short (maximum 22 days), the IMPs are injected only once at 2 different visits and the P03277 doses selected for the current study are within the range of those tested during the phase I study for which no safety alert was identified.

Specific subjects study stopping rules have been set up in the study protocol (see [section 11.2](#)) and check points (see [Study Flow Chart](#)) are done before performing the second MRI.

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

However, a Data Safety Monitoring Board (DSMB) will be set up for assessing the safety of the Investigational Medicinal Product (IMP) during the study and for monitoring the overall conduct of the clinical trial as well as ensuring that the subjects stopping rules for safety reasons are applied when required.

The DSMB members will be: the international coordinator and Guerbet team (drug safety physician, Medical Expert, clinical project manager and ad-hoc team members). All the members will remain blinded regarding all the study data. The role and responsibilities of this DSMB will be described in a separate document (Data Safety Monitoring Plan).


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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: 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
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1) Current Step 4 version dated 5 February 1998
- 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
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals
- Regional / local regulations

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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 an 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 Investigator Site File (ISF).

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 inconveniences 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.

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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, according to local regulation.

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 form or of any other document to be provided to the subjects and approved by the Sponsor, 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 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.

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15 QUALITY CONTROL / QUALITY ASSURANCE

15.1 Direct Access to Source Data/Documents

The investigator will allow Guerbet representatives, the persons responsible for audit conduct, 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 not be captured by any medium such as document for biological results, digital supports, ECG tracings etc...

For this study, the following will be considered as source data (as a minimum): subjects medical files, images.

If computerised medical files are used, the investigator must:

- At the start of the study, print, sign and date all the medical files of all subjects,
- During the study, 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, well-being and study data accuracy and completeness.

A representative in charge of monitoring of blinded data and another one in charge of unblinded data review will be involved in the clinical monitoring of the study.

15.3 Clinical Data Handling


15.3.1 Data Reported in the eCRF

The eCRF will allow recording of the data required by the protocol.

The investigator or the designated person from his/her team agrees to complete the eCRF, at each subject visit, and all other documents provided by Guerbet (e.g.; documents relating to the IMP management) and to reply to any raised data clarifications in a timely manner.

The investigator must attest:

- The authenticity of the data collected in the eCRF;

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- The consistence between the data in the eCRF and those in the source documents

15.3.2 Data Reported in the eCRF according to Subject Status

For screening failure, only the date of visit, date of informed consent signature, demographic data, the adverse event and the reason for non-selection will be reported.

For included subjects, withdrawn before the administration of the IMP, only the selection data, the safety data and the reason for 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 eCRF (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.

15.4 Audits and Inspections

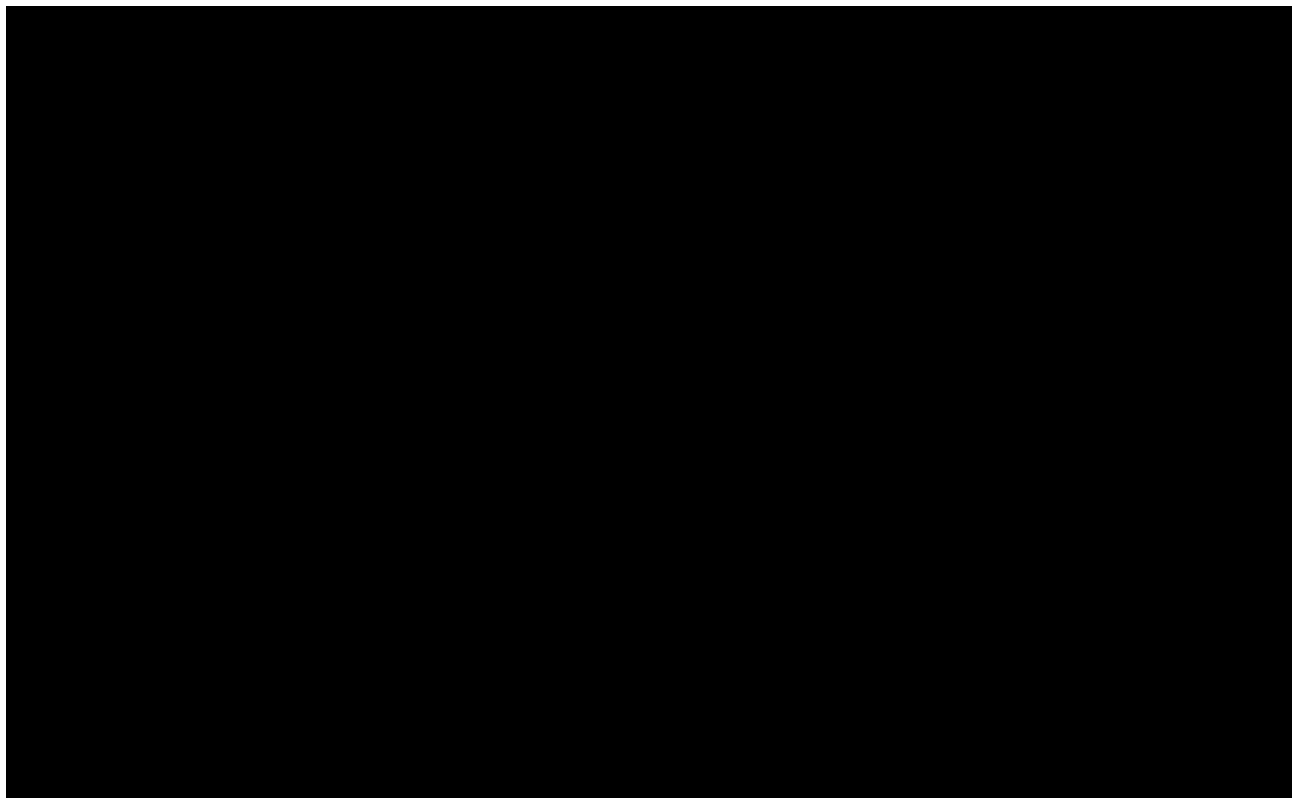
At any time during the study conduct, Guerbet may mandate a representative to perform an audit of investigational sites in order to assess compliance with the regulatory and ethical requirements, the study protocol and related instructions and to assess the accuracy and completeness of data generated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


In parallel, at any time during the study conduct Regulatory/Competent/ 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.




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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 Volume of P03277 injection by dose group and body weight

Adults		Dose (mmol/kg)			
		0.025	0.05	0.1	0.2
		Dose (ml/kg)			
		0.05	0.1	0.2	0.4
Body Weight		Volume	Volume	Volume	Volume
Kilograms (kg)	Pounds (lb)	(mL)	(mL)	(mL)	(mL)
40	88	2	4	8	16
50	110	2,5	5	10	20
60	132	3	6	12	24
70	154	3,5	7	14	28
80	176	4	8	16	32
90	198	4,5	9	18	36
100	220	5	10	20	40
110	242	5,5	11	22	44
120	264	6	12	24	48
130	268	6,5	13	26	52
140	308	7	14	28	56
150	330	7,5	15	30	60

19.2 Volume of MultiHance® injection by dose group and body weight

Adults		Dose (mmol/kg)
		0.1
		Dose (ml/kg)
Body Weight		0.2
Kilograms (kg)	Pounds (lb)	Volume (mL)
40	88	8
50	110	10
60	132	12
70	154	14
80	176	16
90	198	18
100	220	20
110	242	22
120	264	24
130	286	26
140	308	28
150	330	30

