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Efficacy and Safety of gado**PIC**lenol for Cen**T**ral Nervo**U**s System (CNS)

Magnetic **RE**sonance Imaging (MRI)

Phase III Clinical Trial

The PICTURE trial

EudraCT No.: 2018-003988-54

IND No.: 123673

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PROTOCOL SYNOPSIS

Trial Title: Efficacy and Safety of gadopiclenol for Central Nervous System (CNS) Magnetic Resonance Imaging (MRI) Phase III Clinical Trial	
Trial Product(s): G03277	Active Ingredient(s): gadopiclenol
EudraCT No.: 2018-003988-54	IND No.: 123673
Potential Participating countries (Potential Number of sites): Worldwide trial involving approximately 40 sites.	

Trial Objectives

As the trial is a multi-regional one, trial objectives are presented to meet with the respective regulatory authorities' submission purpose.

Primary objective 1:

- To demonstrate the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patient referred for contrast-enhanced MRI of CNS, in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) using the patient as his/her own control.

Primary objective 2:

- To demonstrate the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patient referred for contrast-enhanced MRI of CNS.

For FDA, the primary objective 1 is to be achieved. The primary objective 2 will serve as one of the secondary objectives.

For EMA, both primary objectives 1 and 2 are to be achieved.

Secondary objectives:

- To demonstrate the non-inferiority of gadopiclenol compared to gadobutrol in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patient referred for contrast-enhanced MRI of CNS (for FDA only).
- To assess the following parameters with gadopiclenol and gadobutrol
  - ✓ lesion visualization assessment by investigator
  - ✓ Improvement in lesion visualization scores at patient-level
  - ✓ Technical adequacy of images
  - ✓ Number, size and location of lesions
  - ✓ Diagnostic confidence
  - ✓ Impact of contrast-enhanced MRI on patient treatment plan
  - ✓ Contrast to Noise Ratio (CNR)

- ✓ Percentage enhancement (E%) of lesion(s)
- ✓ Lesion to Background Ratio (LBR)
- ✓ Overall diagnostic preference

- To assess the safety profile of gadopiclenol and gadobutrol

Trial design and methodology

The trial has a prospective, multi-center, randomized, double-blind, controlled and cross-over design.

The Investigational Medicinal Products (IMPs) used during the trial are gadopiclenol and gadobutrol.

The primary criteria 1 will compare gadopiclenol-enhanced MRI (pre + post images = paired images) to unenhanced MRI (pre images), using the patient as his/her own control.

The primary criteria 2 will compare gadopiclenol-enhanced MRI (paired images) to gadobutrol-enhanced MRI (paired images).

Patients, once informed consent form (ICF) signed, will perform a screening visit (V1) to confirm trial eligibility, then will be randomized in the trial to determine the order of IMP injection. Each of the 2 MRI visits (V2 and V4) will be followed by a safety visit (V3 and V5) performed 1 day after the MRI visit.

Two MRIs will be obtained for each patient: gadopiclenol-enhanced MRI and gadobutrol-enhanced MRI (see Figure 1), however the nature of the contrast agents injected at Visit 2 and at Visit 4 will be randomly assigned by Interactive Web Response System (IWRS).

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

The randomization scheme will allocate patients in a 1:1 ratio to the two arms, gadopiclenol-gadobutrol or gadobutrol-gadopiclenol.

For each investigational site, at least one experienced neuroradiologist or radiologist experienced in MRI of CNS will be appointed at the start of the trial to read all images of patients included at the site (on-site read).

In addition, 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 blinded image evaluations (off-site read) will be performed by 3 independent blinded radiologists for the reading of random images and by 3 additional independent blinded radiologists for the global pairs assessment. An imaging electronic Case Report Form (eCRF) will be used to ensure that the images are properly aligned and to ensure that all necessary data for the trial purpose are documented by the independent blinded readers.

To allow exact matching of lesions between imaging modalities (Pre and Paired), between the two MR examinations with gadopiclenol and gadobutrol, and among 3 readers, an independent radiologist (lesion tracker) will perform lesion tracking, separate from the image evaluation by the investigator and by the independent blinded readers.

The IWRS will be used to randomize order of contrast agents to be injected, to allocate IMPs, to calculate the volume of IMP to be administered based on the body weight and to record patient's visits.

During the trial, the safety will be monitored and assessed based on the reporting of adverse events (AEs), the results of vital signs measurement, the injection site tolerance evaluation and the clinical laboratory parameters (blood samples).

Number of patients: 250

Eligibility criteria

Inclusion criteria:

1. Female or male adult patient (patient having reached legal majority age).
2. Patient presenting with known or highly suspected CNS lesion(s) with focal areas of disrupted Blood Brain Barrier (BBB) (e.g., primary and secondary tumors) based on results of a previous imaging procedure such as Computed Tomography (CT) or MRI, which should have been performed within 12 months prior to ICF signature.
3. Patient scheduled for a CNS contrast-enhanced MRI examination for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the trial.
4. If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of remaining lesion(s) on the basis of available clinical information.
5. Patient able and willing to participate in the trial.
6. Patient having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.
7. Patient affiliated to national health insurance according to local regulatory requirements.

To be included in the trial, the patient must meet all the inclusion criteria.

Non-inclusion criteria:

1. Patient presenting extra cranial lesions and/or extra-dural lesions.
2. Patient presenting with an acute relapse of multiple sclerosis as qualifying CNS lesion.
3. Patient presenting with known class III/IV congestive heart failure according to the New York Heart Association classification (NYHA).
4. Patient having received any investigational medicinal product within 7 days prior to trial entry or scheduled to receive any investigational treatment in the course of the trial.
5. Patient presenting with any contraindication to MRI examinations.
6. Patient previously randomized in this trial.
7. Patient having received any contrast agent (MRI or CT) within 3 days prior to first trial product administration, or scheduled to receive any contrast agent during the course of the trial or within 24 hours after the second trial product administration.

8. Patient expected/scheduled to have any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc…) that may impact the aspects of the imaged lesions between the 2 MRI examinations. (Patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included).
9. Patient with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate in the trial.
10. Patient unlikely to comply with the protocol, e.g. uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the trial.
11. Patient related to the investigator or any other trial staff or relative directly involved in the trial conduct.

Non-inclusion criteria to be checked at V1, V2 and V4:

12. Patient presenting with acute or chronic renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² assessed within 1 day prior to each contrast agent injection.
13. Pregnant or breast-feeding female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative urine pregnancy test within 1 day prior to trial MRI and must be using a medically approved contraception method until the last trial visit).
14. Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other GBCAs (such as hypersensitivity, Post contrast acute kidney injury).

Patients presenting with one or more of the non-inclusion criteria must not be included in the trial.

The diagnosis obtained from previous (qualifying) imaging examinations will be considered as medical history to assess inclusion criteria. All the trial efficacy analyses will be only based on the images obtained through the trial MRI.

Investigational Medicinal Product(s) administration

Investigational Medicinal Product (IMP) 1:

- gadopiclenol, single intravenous (IV) bolus injection at 0.05 mmol/kg BW

Investigational Medicinal Product (IMP) 2:

- gadobutrol, single intravenous (IV) bolus injection at 0.1 mmol/kg BW

For both products, the recommended injection rate is 2 mL/second followed by a saline flush via manual injection or power injector.

Trial duration for patients:

Minimum trial duration for patients: 4 days (if V1 and V2 done on the same day) and the second MRI is done 2 days after the first one.

Maximum trial duration for patients: 23 days if the screening period lasts 7 days and the second MRI is done 14 days after the first one.

The trial includes a maximum of 5 visits:

- One screening visit (V1) up to 7 days prior to inclusion (V1 could be done on the same day as the randomization visit (V2) if all the inclusion/non-inclusion criteria are met).
- Two sequential imaging visits (V2 and V4, minimum interval 2 days and up to 14 days): each visit will consist of gadopiclenol injection or gadobutrol injection and MRI procedure.
- Two safety visits (V3 and V5): 1 day after each injection and MRI examination.

The trial will be considered as completed once all the images collected for all the patients will have been reviewed by all the independent blinded readers. The patient's participation is defined as the period from the screening visit (ICF signature) to the last trial visit.

Evaluation criteria

Primary criteria 1:

- Lesion visualization (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement) will be assessed by 3 independent off-site blinded readers on Paired (pre+post) images versus Pre images for gadopiclenol using a 4-point scale (off-site read)

Primary criteria 2 (for EMA, secondary criteria for FDA):

- Lesion visualization (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement) will be assessed by 3 independent off-site blinded readers on Paired (pre+post) images for gadopiclenol as compared to gadobutrol using a 4-point scale (off-site read).

The evaluation for the primary criteria will be performed for up to the 3 most representative lesions. Representative lesion is defined according to lesion size and contrast enhancement. For pre-contrast images read, as contrast enhancement cannot be completely foreseen, 3 largest potentially enhancing lesions should be selected. For paired images read, 3 largest enhancing lesions should be prioritized.

The 3 co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) will be assessed and the mean of scores for each of the 3 co-primary criteria will be calculated as follows:

Mean of scores = score of the lesion 1 + score of the lesion 2 (if any) + score of the lesion 3 (if any)) divided by the number of lesions (up to 3 most representative lesions).

For each reader, only matching lesion between Paired images and Pre images will be considered for the purpose of the primary criteria 1 evaluation and only matching lesion between Paired images of gadopiclenol and gadobutrol will be considered for the purpose of the primary criteria 2 evaluation.

For each reader, if the MR images are not assessable or if no matching lesion between Paired images and Pre images is identified, then the patient will not be included in the primary criteria 1 evaluation. In the same way, if the MR images are not assessable or if no matching lesion between Paired images of gadopiclenol and gadobutrol is identified, then the patient will not be included in the primary criteria 2 evaluation.

The mean of scores for each of the lesion visualization co- primary criteria and for each reader will range from 1 to 4.

Secondary criteria:

The following parameters will be evaluated with gadopiclenol and gadobutrol:

- Same as primary criteria 2, lesion visualization (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement) for gadopiclenol as compared to gadobutrol (off-site read) (For FDA only).
- Improvement in lesion visualization scores at patient-level: a comparison of paired images to pre images with respect to the proportion of patients who have paired image scores that are greater ("better"), or same/worse ("not better") than the pre images.
- Lesion visualization (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement) (on-site read)
- Technical adequacy of images (on-site and off-site read)
  Images will be evaluated as technically adequate for diagnosis and assessable or not.
- Number, size and location of lesions (on-site and off-site read)
  Number, size and location of lesions detected will be recorded for each patient.
- Diagnostic confidence (on-site and off-site read)
  Degree of confidence will be assessed using a 5 point-scale.
- Impact of contrast-enhanced MRI on patient treatment plan (on-site read)
  Assessment of potential impact of on-site images reading, at V2 and V4, on patient treatment plan.

The 3 quantitative criteria (CNR, E%, LBR) will be calculated by patient in averaging the parameter for maximum 3 most representative lesions (off-site read).

- Contrast to Noise ratio (CNR)

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

where SI_{lesion} = Signal intensity of lesion.
SI_{ht} = Signal intensity of healthy tissue (brain or spinal cord).
SD_{noise} = Standard Deviation (SD) of background noise.

- Percentage enhancement (E%) of lesion(s) (off-site read).

$$E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \text{x} 100$$

where SI_{post} = Signal intensity of lesion on post injection images.
SI_{pre} = Signal intensity of lesion on pre injection images.

- Lesion to Background Ratio (LBR) (pre and post)

$$\text{LBR} = \frac{SI_{lesion}}{SI_b}$$

where SI_{lesion} = Signal intensity of lesion.
SI_b = Signal intensity of background (healthy tissue in brain or spinal cord).

- Overall diagnostic preference (off-site read)
  The evaluation will be performed in a global matched-pairs fashion and preference will be determined on a 3-point scale. Reason for preference will also be recorded.
- Safety profile of gadopiclenol and gadobutrol
  The safety assessments will be based on the reporting of adverse events (AEs), the results of

vital signs measurement, the injection site tolerance evaluation and the clinical laboratory parameters (blood samples).

Statistical methods

Primary objective 1 (superiority of Paired images versus Pre images of gadopiclenol MR examination regarding lesion visualization co-primary criteria)

For gadopiclenol, the difference "Paired" -"Pre" for each of 3 co-primary criteria will be analyzed using paired t-tests on matching lesions. Results will be presented per reader.

To be successful, 2 out of 3 readers will have to meet the alternative hypothesis for the three co-primary criteria in the gadopiclenol group: a statistically significant (one-sided $p \geq 0.025$) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions simultaneously.

Sample size assessment for the Primary objective 1:

Expecting that for each co-primary criteria, the difference in mean scores will be 0.35, *Gutierrez et al. 2015*, (["Paired" – "Pre"] within patient mean of lesion scores) with 1.5 standard deviation, a sample of 200 patients in the gadopiclenol group will have 90% power when using a single group superiority t-test with a 0.025 one-sided significance level.

As 20% drop-out rate is expected, sample size increases to 250 patients with CNS lesions.

Primary objective 2 non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria):

The Student's t-based two-sided 95% confidence intervals of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 co-primary criteria using matching lesions only. If the lower bound of this confidence interval is above the non-inferiority margin set to 0.35 for at least 2 out of 3 readers and for the 3 co-primary criteria simultaneously, then non-inferiority between gadopiclenol and gadobutrol will be concluded.

As soon as the non-inferiority is demonstrated, the superiority of the gadopiclenol over gadobutrol will be tested using the same method. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

Sample size for the primary objective 2:

- Non-inferiority margin:

For EMA, both primary objectives 1 and 2 are to be achieved therefore this trial will provide a direct demonstration of the superiority of Paired images with gadopiclenol over unenhanced images (objective 1). So, it can be considered as three-armed trial design with unenhanced images as placebo as described in *EMA guideline on the choice of the non-inferiority margin*. As such, it is not necessary to define a value for non-inferiority margin to establish that gadopiclenol has efficacy over unenhanced images.

A 10% non-inferiority margin was considered clinically as an unimportant difference and therefore relevant to establish acceptable efficacy relative to gadobutrol (objective 2). Based on the Guerbet Phase IIb GDX-44-004 clinical trial results on lesion visualization co-criteria, the mean score for each of the 3 co-criteria is expected to be equal to 3.5. So the margin is set to 0.35 (10%).

- Sample size hypothesis:

An enrollment of 200 patients is deemed necessary for the lower limit of the 95% CI to exceed the

non-inferiority margin set to 0.35, assuming 80% power and for each co-primary criterion, the expected difference in mean scores is 0 with an expected standard deviation of 1.75.

If one assumed a patient drop-out rate of 20%, a minimum enrollment of 250 patients with CNS lesions is planned.

Therefore, a total number of 250 patients will allow a sufficient power to meet both objectives.

TRIAL FLOW CHART

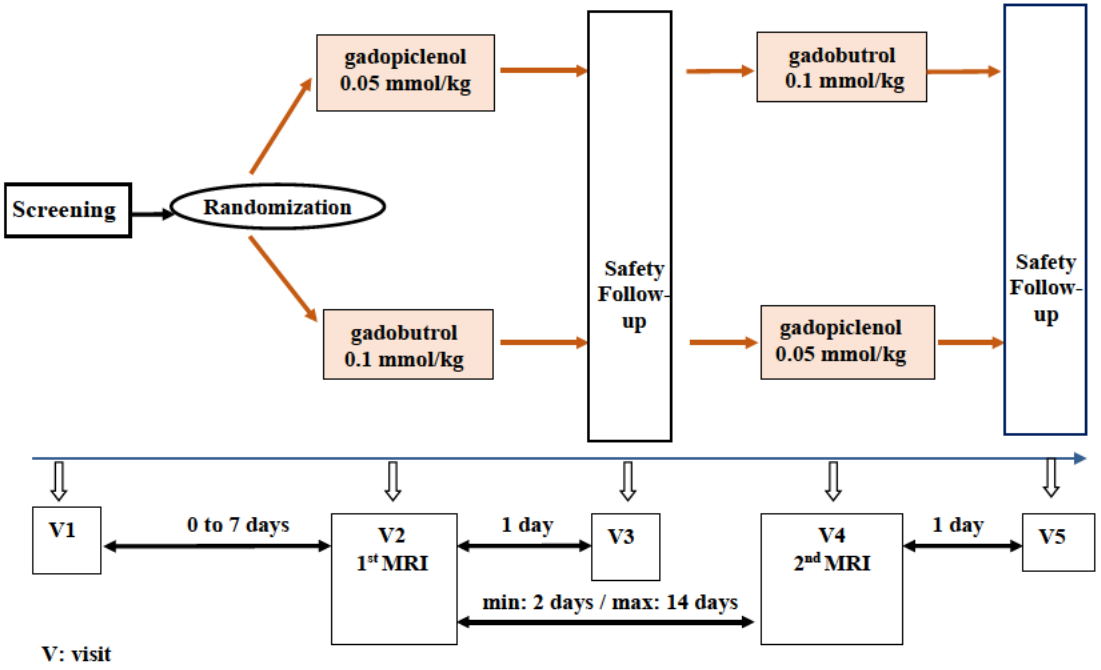
Table 1: Trial flow chart

Visit [1]	**V1**	**V2**			**V3**	**V4**			**V5**
Evaluation/ procedure	**Screening**	**Randomization 1st contrast injection Baseline** [10]			**Safety follow up Post injection**	**2nd contrast injection (2 days up to 14 days post V2)**			**Safety follow up Post injection**
Time Point	**≤7 days**	**Prior to MRI**	**MRI**	**60± 15min**	**1 day after V2**	**Prior to MRI**	**MRI**	**60± 15min**	**1 day after V4**
Informed consent signature	X								
Eligibility criteria	X	X				X[11]			
Demographic data and height	X								
Medical history including CNS disease[12]	X								
Contrast Agents intolerance history	X								
Physical examination[2]	X								
Body weight		X				X			
Concomitant treatments	X								
Pregnancy test [3]	X	X[3]				X			
Local creatinine and eGFR evaluation[4]		X			X	X			X
Clinical laboratory parameters [5]		X			X	X			X
Vital signs (BP, PR) [6]		X		X	X	X		X	X
IMP injection			X				X		
Images acquisition			X				X		
IWRS [7]	X	X			X	X			X
Injection-site tolerance[8]			X	X	X		X	X	X
Adverse events (AEs)[9]	X								
Procedures/Therapeutic measures	X								

(1) V1 can be performed on the same day as V2. MRI procedures, at V2 and V4, should be performed on the same day as IWRS connection and contrast agent injection.
(2) Physical examination should be performed by a physician: examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information indicating the global assessment (normal or abnormal (specify)) of the physical examination should be recorded on source documentation.
(3) Urine pregnancy test (if applicable) is to be done on site. At V2 and V4, results must be available prior to IWRS connection and administration of IMP. In case V1 and V2 are performed on the same day, only one pregnancy test is required.
(4) At V2 and V4, eGFR is to be evaluated locally, and results must be available prior to IWRS connection and administration of IMP. Starting at V3, change in local serum creatinine result should be checked as per ESUR guidelines (see section 7.2.10). The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient.
(5) Clinical laboratory parameters will be analysed by the central laboratory: haematology and biochemistry, see section 8.5 for details
(6) Vital signs: BP: blood pressure (supine systolic and diastolic), PR: Pulse Rate
(7) IWRS: connection should be done at each trial visit and in case of screening failure or premature discontinuation
(8) Injection-site tolerance (pain, eruption, extravasation, inflammation, or other) is to be assessed during the injection, 60 ± 15 min and 1 day post injection.
(9) AEs occurring during the time of the patient's participation in the trial, must be reported and followed, unless they meet the following definition: the events which occur before the first IMP administration, and which are not serious and not related to the trial procedures can be recorded as medical history upon the investigator's judgement. Procedures/therapeutic measures for AE are also to be reported.
(10) All the assessments performed prior to the first MRI at V2 will be considered as baseline value.
(11) Some non-inclusion criteria must be checked again at V4 (see section 4.2).
(12) In case brain metastasis is the trial disease, the corresponding primary cancer will be reported in medical history

TRIAL DIAGRAM

Figure 1:trial diagram



SIGNATURE PAGE

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical
BBB	Blood Brain Barrier
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BW	Body weight
CI	Confidence Interval
CNS	Central Nervous System
CRA	Clinical Research Associate
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
E%	Percentage enhancement of lesion
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ESUR	European Society of Urogenital Radiology
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
Gd	Gadolinium
GRE	Gradient Echo
IBR	Independent Blinded Reader
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

INV	Investigator
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
IWRS	Interactive Web Response System
LBR	Lesion to Background Ratio
LDH	Lactate Dehydrogenase
MCV	Mean red blood Cells Volume
MRI	Magnetic Resonance Imaging
NPS	Numeric Pain intensity Scale
NSF	Nephrogenic Systemic Fibrosis
PC-AKI	Post-Contrast-Acute Kidney Injury
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Pulse Rate
PT	Preferred Term
RBCs	Red Blood Cells
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Spin Echo
SI	Signal Intensity
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SS	Safety Set
SPS	Screened Patient Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TSE	Turbo Spin Echo
WBCs	White Blood Cells

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AMENDMENT

Not Applicable

1 INTRODUCTION

1.1 Trial Rationale

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

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

The ability of gadopiclenol to be a MRI contrast agent has been demonstrated by its at least two-fold higher T1 relaxivity compared to other available Gd-based contrast agents (GBCA). A proof of concept has been obtained for the efficacy of gadopiclenol as a MRI contrast agent for central nervous system (CNS) imaging in a model of brain tumor implanted in rats as well as during the phase IIa clinical trial. The safe and lowest effective clinical dose identified in phase IIb trial is 0.05 mmol/kg body weight (BW) based on comparison with gadobenate dimeglumine (MultiHance®) for the contrast-to-noise ratio (CNR) assessed as primary endpoint.

One phase I/IIa trial and one phase IIb trial have been completed, with 304 patients exposed to gadopiclenol.
On the basis of the extensive nonclinical study program and the PK/ clinical safety data available from phase I/IIa and phase IIb trials, it is considered that there are sufficient guarantees to ensure the safety of gadopiclenol administration in adult and pediatric (from 2 to 17 years) patients at a single dose.

At the launch of the phase III program and based on the initial clinical studies, the administrations of the gadopiclenol were well tolerated. More details on the safety are provided in the investigator's brochure in force that is the reference safety information for the gadopiclenol. Likewise, the SmPC is the reference safety information for gadobutrol.

1.2 Background

The use of GBCAs has revolutionized the radiologic field since their introduction 30 years ago. These contrast agents have been used extensively in a large range of indications, particularly MRI examinations of Central Nervous System (CNS). Contrast enhancement has enabled improving tissue contrast and lesion characterization and more sensitive detection of even very small lesions. Contrast-enhanced MRI of brain lesions also plays a vital role during the post-therapeutic or intervention phase in determining treatment response: early identification of the lack of treatment efficacy can facilitate selection of an alternative therapeutic approach, potentially improving patient outcomes

Pathologies of the CNS represent the most important indication in MRI. It is a well-established technique and more than 50% of CNS MR examinations are performed after intravenous (IV) injection of a GBCA. For MR Imaging of CNS, the GBCAs already commercialized exhibit a range of r1 and r2 relaxivity values providing their efficacy at a clinical dose at 0.1 mmol/kg BW. Optimal detection and characterization of CNS lesions on contrast-enhanced T1-weighted MR imaging depends as much on the contrast agent used as on the sequence parameters applied for image acquisition. The increased R1 relaxivity leads to increased signal intensity enhancement and thus significantly improved lesion visualization and better depiction of morphologic features for CNS lesions [1-8]. High relaxivity GBCA may potentially enable earlier detection of small cerebral or spinal metastasis, or detect more tiny lesions which may be overlooked by other GBCAs.

1.3 Benefit/Risk Assessment

The results of the clinical trial phase IIa suggest that gadopiclenol have potential effectiveness as a contrast agent for MRI and is safe and well tolerated in patients with brain lesions up to a dose of 0.2 mmol/kg. The phase IIb trial demonstrated the efficacy of gadopiclenol for CNS imaging in patients with brain lesions as well as the good safety profile of the product.

2 TRIAL OBJECTIVES

As the trial is a multi-regional one and in order to meet with the respective requirements of regulatory authorities within one single protocol, trial objectives are presented with reference to the regulatory authorities..

2.1 Primary Objectives

Primary objective 1:

- To demonstrate the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patient referred for contrast-enhanced MRI of CNS, in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) using the patient as his/her own control.

Primary objective 2:

- To demonstrate the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patient referred for contrast-enhanced MRI of CNS.

For FDA, the primary objective 1 is to be achieved. The primary objective 2 will serve as one of the secondary objectives.

For EMA, both primary objectives 1 and 2 are to be achieved.

2.2 Secondary Objectives

- To demonstrate the non-inferiority of gadopiclenol compared to gadobutrol in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patient referred for contrast-enhanced MRI of the CNS (idem primary objective 2, considered as secondary objective for FDA).
- To assess the following parameters with gadopiclenol and gadobutrol
  - ✓ lesion visualization assessment by investigator
  - ✓ Improvement in lesion visualization scores at patient-level
  - ✓ Technical adequacy of images
  - ✓ Number, size and location of lesions
  - ✓ Diagnostic confidence
  - ✓ Impact of contrast-enhanced MRI on patient treatment plan
  - ✓ Contrast to Noise Ratio (CNR)
  - ✓ Percentage enhancement (E%) of lesion(s)
  - ✓ Lesion to Background Ratio (LBR)
  - ✓ Overall diagnostic preference
- To assess the safety profile of gadopiclenol and gadobutrol

3 TRIAL DESCRIPTION

3.1 Protocol Design

The trial has a prospective, multi-center, randomized, double-blind, controlled and cross-over design.

The IMPs used during the trial are gadopiclenol and gadobutrol.

The primary criteria 1 will compare gadopiclenol-enhanced MRI (pre + post images = paired images) to unenhanced MRI (pre images), using the patient as his/her own control.

The primary criteria 2 will compare gadopiclenol-enhanced MRI (paired images) to gadobutrol-enhanced MRI (paired images).

Patients, once informed consent form (ICF) signed, will perform a screening visit (V1) to confirm trial eligibility, then will be randomized in the trial to determine the order of IMP injection. Each of the 2 MRI visits (V2 and V4) will be followed by a safety visit (V3 and V5) performed 1 day after the MRI visit.

Two MRIs will be obtained for each patient: gadopiclenol-enhanced MRI and gadobutrol-enhanced MRI (see Figure 1), however the nature of the contrast agents injected at Visit 2 and at Visit 4 will be randomly assigned by IWRS.

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

The randomization scheme will allocate patients in a 1:1 ratio to the two arms, gadopiclenol-gadobutrol or gadobutrol-gadopiclenol.

For each investigational site, at least one experienced neuroradiologist or radiologist experienced in MRI of CNS will be appointed at the start of the trial to read all images of patients included at the site (on-site read).

In addition, 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 blinded image evaluations (off-site read) will be performed by 3 independent blinded radiologists for the reading of random images reading and by 3 additional independent blinded radiologists for the global pairs assessment. An imaging electronic Case Report Form (eCRF) will be used to ensure that the images are properly aligned and to ensure that all necessary data for the trial purpose are documented by the independent blinded readers.

To allow exact matching of lesions between imaging modalities (Pre and Paired), between the two MR examinations with gadopiclenol and gadobutrol, and among 3 readers, an independent radiologist (lesion tracker) will perform lesion tracking, separate from the image evaluations.by the investigator and by independent blinded readers.

The IWRS will be used to randomize order of contrast agents to be injected, to allocate IMPs, to calculate the volume of IMP to be administered based on the body weight and to record patient's visits.

During the trial, the safety will be monitored and assessed based on the reporting of adverse events (AEs), the results of vital signs measurement, the injection site tolerance evaluation and the clinical laboratory parameters (blood samples).

3.2 Justification for dose

Based on Phase IIb results, gadopiclenol dose of 0.05mmol/kg BW, is deemed to be as efficient as all other available GBCAs at clinical dose of 0.1mmol/kg BW. It will be investigated for diagnostic efficacy in terms of lesion visualization in patients with CNS pathologies.

Gadobutrol will be used, as an active comparator, at its standard approved dose of 0.1 mmol/kg BW.

3.3 Trial Duration

3.3.1 *Duration of patient's participation*

Minimum trial duration for patients: 4 days (if V1 and V2 done on the same day) and the second MRI is done 2 days after the first one.

Maximum trial duration for patients: 23 days if the screening period lasts 7 days and the second MRI is done 14 days after the first one.

The trial includes a maximum of 5 visits:

- One screening visit (V1) up to 7 days prior to inclusion (V1 could be done on the same day as the randomization visit (V2) if all the inclusion/non-inclusion criteria are met).
- Two sequential imaging visits (V2 and V4, minimum interval 2 days and up to 14 days): each visit will consist of a gadopiclenol injection or gadobutrol injection and MRI procedure.
- Two safety visits (V3 and V5): 1 day after each injection and MRI examination.

3.3.2 *End of trial*

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

The patient's participation is defined as the period from the screening visit (ICF signature) to the last trial visit.

3.4 Interim Analysis

Not applicable

3.5 Trial Committee(s)

Not applicable (see Section 12).

4 PATIENT SELECTION

Prospective approval of any types of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

To be included in the trial, the patient must meet all these inclusion criteria.

1. Female or male adult patient (patient having reached legal majority age).
2. Patient presenting with known or highly suspected CNS lesion(s) with focal areas of disrupted Blood Brain Barrier (BBB) (e.g., primary and secondary tumors) based on results of a previous imaging procedure such as Computed Tomography (CT) or MRI, which should have been performed within 12 months prior to ICF signature.
3. Patient scheduled for a CNS contrast-enhanced MRI examination for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the trial.
4. If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of remaining lesion(s) on the basis of available clinical information.
5. Patient able and willing to participate in the trial.
6. Patient having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.
7. Patient affiliated to national health insurance according to local regulatory requirements.

4.2 Non-Inclusion Criteria

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

1. Patient presenting extra cranial lesions and/or extra-dural lesions.
2. Patient presenting with an acute relapse of multiple sclerosis as qualifying CNS lesion.
3. Patient presenting with known class III/IV congestive heart failure according to the New York Heart Association classification (NYHA).
4. Patient having received any investigational medicinal product within 7 days prior to trial entry or schedule to receive any investigational treatment in the course of the trial.
5. Patient presenting with any contraindication to MRI examinations.
6. Patient previously randomized in this trial.
7. Patient having received any contrast agent (MRI or CT) within 3 days prior to first trial product administration, or scheduled to receive any contrast agent during the course of the trial or within 24 hours after the second trial product administration.
8. Patient expected/scheduled to have any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc…) that may impact the aspects of the imaged lesions between the 2 MRI examinations. (Patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included).

9. Patient with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate in the trial.
10. Patient unlikely to comply with the protocol, e.g. uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the trial.
11. Patient related to the investigator or any other trial staff or relative directly involved in the trial conduct.

Non-inclusion criteria to be checked at V1, V2 and V4:

12. Patient presenting with acute or chronic renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² assessed within 1 day prior to each contrast agent injection.
13. Pregnant or breast-feeding female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative urine pregnancy test within 1 day prior to trial MRI and must be using a medically approved contraception method* until the last trial visit).
14. Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other GBCAs (such as hypersensitivity, Post contrast acute kidney injury).

** medically approved contraception methods include: abstinence (defined as refraining from heterosexual intercourse during the entire trial), female sterilization (sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy), combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the female patient and that the vasectomised partner has received medical assessment of the surgical success.)*
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

The diagnosis obtained from previous (qualifying) imaging examinations will be considered as medical history to assess inclusion criteria. All the trial efficacy analyses will be only based on the images obtained through the trial MRI.

4.3 Patient Identification

After having signed the written informed consent patients will be allocated a unique Identification Number (Patient ID).

Any patient who has signed an informed consent will be considered as a 'screened' patient.

This Patient ID will contain 8 digits: the first three digits corresponding to the country number (code ISO 3166-1 numeric) the following two digits corresponding to the site number, which are attributed at the beginning of the trial, and the last three digits being chronologically implemented depending on patient screening. The lowest screening number will correspond to the first patient screened at this site and the highest number to the last patient screened.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

Investigational Medicinal Product(s) (IMP) 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 1 vial packaged in a carton box with a single use detachable label that will allow ensuring accuracy of IMP allocation per patient.

5.1 Investigational Medicinal Product(s) Description

5.1.1 *Investigational Medicinal Product 1*

Name: gadopiclenol [redacted]

Pharmaceutical form: vial of 20 ml

Gadopiclenol 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

Route and method of administration: single intravenous (IV) bolus injection at a recommended rate of 2 mL/second followed by a saline flush via manual injection or power injector.

Dose per administration: dose/volume of gadopiclenol to be administered will be calculated by IWRS based on patient's weight at the dose of 0.05 mmol/kg BW. Volume to be injected will be rounded to the nearest whole number as described in section 5.6.

Sufficient IMP must be allocated to one patient by IWRS.

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

5.1.2 *Investigational Medicinal Product 2*

Name: gadobutrol

Pharmaceutical form: vial of 15 ml

Gadobutrol is an aqueous solution. Each vial contains 15 mL of solution presented as a sterile, clear, ready-to-use solution for injection.

Concentration: 1 M

Route and method of administration: single intravenous (IV) bolus injection at a recommended rate of 2 mL/second followed by a saline flush via manual injection or power injector.

Dose per administration: dose/volume of gadobutrol to be administered will be calculated by IWRS based on patient's weight at the dose of 0.1 mmol/kg BW. Volume to be injected will be rounded to the nearest whole number as described in section 5.6.

Sufficient IMP must be allocated to one patient by IWRS.

Please refer to the SmPC of gadobutrol for more information on the product.

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 gadopiclenol and gadobutrol will be performed by Guerbet (or its designee).

The outer packaging will be the same for both products 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, batch number and patient number. This label will be stuck on the patient file or trial documentation.

IMP will consist in a box that contains one 20 ml vial of gadopiclenol or one 15 ml vial of gadobutrol.

In case of issue related to IMP (damaged, broken vials…), a new IMP will be allocated to the patient 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 trial completion, all used (including empty vials) and unused IMPs should have been returned to Guerbet or to the predefined location for storage before destruction.

5.3 Condition of Investigational Medicinal Product Allocation

5.3.1 *Investigational Product(s) Allocation / Randomization*

At visit 2, the patients will be randomly assigned to one series of 2 MRIs performed each at two trial visits separated by a wash out period of 2 days minimum and up to 14 days. One series consists of the use of gadopiclenol, single intravenous (IV) bolus injection, as contrast agent at visit 2 and gadobutrol, single intravenous (IV) bolus injection, at visit 4 and reverse order for the second series (see Figure 1).

The randomization scheme will allocate patients in a 1:1 ratio to the two trial arms, gadopiclenol-gadobutrol or gadobutrol-gadopiclenol.

The randomization to determine the order of injection at visit 2 and visit 4 will be done via IWRS and performed in blocks to prevent unequal treatment allocation.

The trial design and the injection of the IMPs require identifying before the trial start, two separate teams in each trial 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 patient's file all the unblinded information related to the IMPs and will have to complete dedicated restricted field in clinical eCRF pages.

During the course of the trial, the two teams should not exchange any information regarding the IMPs (nature of IMP injected, order of administration,). The patients' files with unblinded data should not be

filed with the patient's medical and trial 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 patient recruitment progress of a given investigational site. The site should ensure to have enough IMPs before including a new patient. 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.

At visit 2 and visit 4, once all the inclusion /non-inclusion criteria, including 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 patient), 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 situation is under control again. Detailed instructions can be found in the IWRS manual provided to the sites.

5.3.2 *Double-Blind Conditions*

To ensure that administration of the IMP is carried out under double-blind conditions, an unblinded team (nurse, technician or physician) will be responsible for preparing and administrating the IMP(s). This person will ensure non-disclosure of information. He /she will stick the detachable label of the vial into the Patient's records or appropriate form. He /she will also write his/her name, date and signature and the patient number on the box, and after use, he/she will close the box with a seal.

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

Image readings of all patients will be evaluated in blinded conditions regarding the contrast agent injected, as described in Section 8.4.

5.3.3 *Individual Trial Treatment Unblinding*

In case of an adverse event occurring for a patient and which nature would require immediate knowledge of the allocated IMP, the individual trial treatment may be unblinded, if absolutely necessary for the safety of the patients and if unblinding impacts the management of medical cares (see section 9.5).

Conditions and procedure for breaking the code will be reviewed with the investigator and his/her team during the initiation visit.

The persons authorized to unblind trial product during the trial usually are: the investigators and Guerbet Pharmacovigilance physician/officer and European Qualified Person for Pharmacovigilance (EU-QPPV).

If the Clinical Project Manager receives an external request for unblinding (Authorities, health care professionals taking care of the patient, etc.), he/she must inform Guerbet Pharmacovigilance physician/officer.

If the investigator and Guerbet Pharmacovigilance physician/officer unblind the trial product via the IWRS, he/she must inform the Clinical Project Manager as soon as possible but shall not reveal the nature of the trial product in order to protect as much as possible the double-blind design of the trial.

Unblinding must be documented by indicating the patient's identification number, age and sex, the date, time and the reason for unblinding, the identity of the person who performed the unblinding.

Please refer to Section 9.5 for detailed information on patient safety monitoring.

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 trial 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 trial protocol, or dispose of IMP in any other manner.

5.5 Auxiliary Medicinal Product(s) and Other Trial Products

Not applicable

5.6 Trial Product(s) Compliance and Accountability

An unblinded third party, hospital pharmacist, or other allowed personnel, designated by the investigator, 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 patient.

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

The volume (mL) of IMP to be injected to the patients will be determined by IWRS. The volume will be automatically rounded by the system as per the following rule:

- If decimal is < 0.5, volume is rounded to the inferior value (e.g.: from 15.4 mL to 15 mL)
- If decimal is ≥ 0.5, volume is rounded to the superior value (e.g.: from 15.8 mL to 16 mL)

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6 CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

Any medication, including contraception, homeopathic products, pre medication, over-the-counter medications, as well as prescription drugs, on-going at the time of patient's informed consent signed or administered during the trial will be recorded in the patient's medical file and clinical electronic Case Report Form (eCRF). The following information must be provided:

- Drug (brand name or generic name)
- Route of administration
- Purpose (medical history/trial disease/AE/pre-medication/contraception/prophylaxis)
- Indication
- Start/end period: before first administration, between first and second administration, after second (last) administration, ongoing at the end of the trial.

6.1.1 *Concomitant Medications of Special Attention*

Currently, no treatment has been identified that is capable of preventing an allergic reaction with any GBCAs. Thus, no pre-treatment of any nature will be recommended before contrast-enhanced MRI. Nevertheless, if the investigator decides to premedicate a patient, the treatment must be documented in the medical file and then in the clinical 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 patient 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 trial. However warnings and precautions for use of the concomitant treatments taken by the patient should be considered.

In addition, no significant change should occur in any treatment or medical procedure (e.g. chemotherapy, radiotherapy, biopsy or surgery etc…) which may impact the appearance of brain lesion between the 2 MRI examinations. However, patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included.

6.1.2 *Prohibited Concomitant Medications*

Any contrast agent (MRI or CT) within 3 days prior to first trial product administration and during the course of the trial or within 24 hours after the second trial product administration are prohibited.

6.2 Concomitant Procedures

Not applicable

7 EVALUATION CRITERIA

An overview of the imaging trial criteria evaluated by the investigator (INV) and the Independent Blinded Readers (IBR) is provided in the Table 2 below:

Table 2: overview of imaging trial criteria

Images	Pre gadopiclenol	Pre gadobutrol	Paired gadopiclenol	Paired gadobutrol	Global matched-pairs
Lesion visualization	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Technical adequacy of images	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Number, Size and location of lesions	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Diagnostic confidence	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Impact of contrast-enhanced MRI on patient treatment plan			INV	INV	
Contrast to Noise ratio (CNR)			IBR	IBR	
Percentage enhancement (E%) of lesion(s)			IBR	IBR	
Lesion to background ratio (LBR)			IBR	IBR	
Overall diagnostic preference					IBR

IBR: independent blinded reader (off-site); INV: investigator (on-site)

The images sets evaluated per patient are described in the Table 3 below:

Table 3: images sets per patient

Image Set Number	Type
1a	Pre images = unenhanced MRI before gadopiclenol injection
2a	Pre images = unenhanced MRI before gadobutrol injection
1b	Paired images = combined unenhanced and gadopiclenol-enhanced MRI (pre+post images)
2b	Paired images = combined unenhanced and gadobutrol-enhanced MRI (pre+post images)

7.1 Primary Criteria (off-site read)

7.1.1 *Primary criteria 1: lesion visualization criteria for gadopiclenol-enhanced MRI compared to unenhanced MRI (off-site read)*

The lesion visualization criteria is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement, assessed on the images acquired during the MRI performed with gadopiclenol.

The IBR will record each of the 3 co-primary criteria for up to 3 most representative lesions. Representative lesion is defined according to lesion size and contrast enhancement. For pre-contrast images read, as contrast enhancement cannot be completely foreseen, 3 largest potentially enhancing lesions should be selected. For paired images read, 3 largest enhancing lesions should be prioritized.

The evaluation will be performed on Paired images (images set 1b) versus Pre images (images set 1a) using a 4-point scale as described below:

- **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 (not based on signal intensity measurement) according to the following scale:

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

The mean of scores for each of the 3 lesion visualization co-criteria will be calculated as follows:

Mean of scores = score of lesion 1 + score of lesion 2 (if any) + score of lesion 3 (if any) divided by the number of lesions (up to 3 most representative lesions).

For each reader, only matching lesion between paired images and pre images will be considered for the purpose of the primary criteria 1 evaluation.

For each reader, if the MR images are not assessable or if no matching lesion is identified between Paired images and Pre images, then the patient will not be included in the primary criteria 1 evaluation.

The mean of scores for each of the lesion visualization co- primary criteria 1 will range from 1 to 4.

7.1.2 *Primary criteria 2: Lesion visualization criteria for gadopiclenol compared to gadobutrol (off-site read).*

Same as primary criteria 1, the lesion visualization criteria is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement assessed on the images acquired during the MRI performed with gadopiclenol and those performed with gadobutrol.

The IBR will record each of the 3 co-primary criteria for up to 3 most representative lesions, on Paired images (images set 1b) performed with gadopiclenol and Paired images (images set 2b) performed with gadobutrol using a 4-point scale .

Definitions of each co-primary criteria and score calculation are provided in section 7.1.1.

For each reader, only matching lesion between paired images of gadobutrol and gadopiclenol will be considered for the purpose of the primary criteria 2 evaluation.

For each reader, if the MR images are not assessable or if no matching lesion is identified on paired images between gadopiclenol and gadobutrol, then the patient will not be included in the primary criteria 2 evaluation.

The mean of scores for each of the lesion visualization co- primary criteria 1 will range from 1 to 4.

7.2 Secondary Criteria

All secondary criteria will be evaluated for gadopiclenol and gadobutrol.

7.2.1 *Lesion visualization criteria for gadopiclenol as compared to gadobutrol (off-site read) for FDA only.*

The criteria is the same as described in section 7.1.2.

7.2.2 *Improvement in lesion visualization scores at patient-level, paired versus pre-contrast images*

Improvement in lesion visualization scores at patient-level is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement assessed on the images acquired during the MRI performed with gadopiclenol and gadobutrol.

For each contrast agent on Pre and Paired images and for the 3 co-primary criteria, the lesion score is calculated and compared between Pre and Paired images. If the lesion score of Paired images is greater than those of Pre images then the Paired image will be classified as “Better”. If the mean score of Paired images is equal or less than those of Pre images then the Paired image will be classified as “Not Better”.

7.2.3 *Lesion visualization (on-site read)*

The lesion visualization criteria is based on 3 co-criteria: border delineation, internal morphology and degree of contrast enhancement assessed on the images acquired during the MRI performed with gadopiclenol and gadobutrol.

The investigator (radiologist) will record each of the 3 co-primary criteria for up to 3 most representative lesions, on Pre and Paired images (images set 1a, 2a, 1b, and 2b) using a 4-point scale.

The 3 co-criteria definition are listed in section 7.1.1

7.2.4 *Technical adequacy of images (on-site and off-site read)*

For each contrast agent, images will be evaluated as technically adequate for diagnosis using a 4-point scales and as assessable or not by investigators and IBR.

The technical adequacy of images will be rated on a 4 point scales:

1 = non diagnostic
2 = poor
3 = fair
4 = good

Images should be evaluated as assessable or not and if not, the reason should be recorded:

1 = Artifacts due to patient
2 = Artifacts due to machine
3 = Injection technical failure
4 = Inadequate anatomic coverage
5= Other, specify

7.2.5 *Number, size and location of lesions (on-site and off-site read)*

The investigator and IBR is to record the following:

- Number of lesions on pre and paired images
- 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
- In case that more than 3 lesions are present, the investigator/IBR has to enter in the clinical/imaging eCRF how many lesions are present (total number)

7.2.6 *Diagnostic confidence (on-site and off-site read)*

The investigator/IBR will record in the clinical/imaging eCRF his/her diagnosis and his/her confidence in diagnosis for each patient for each pre and paired images of each contrast agent according to the 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 Schwannoma Pituitary adenomas Others, to be specified
Tumors **Secondary**	Brain metastasis Spine metastasis
Inflammatory diseases	to be specified
Infectious diseases	Abscess Others, to be specified
Vascular diseases	Stroke Vascular malformation Others, to be specified
Others	To be specified

Diagnostic confidence will be evaluated to determine the level of certainty that the investigator/IBR 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 patient.

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/IBR chooses 'not assessable' for diagnosis, by definition the confidence level is 1 (= very uncertain).

7.2.7 *Impact of contrast-enhanced MRI on patient treatment plan (on-site)*

The impact on patient treatment plan will be assessed by on-site radiologists and will be summarized for each contrast agent**.** 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 set 1b or set 2b), the investigator will have to document if the patient's 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 *Contrast to Noise Ratio (CNR), Percentage Enhancement (E%) of lesion(s), lesion to Background Ratio (LBR) (off-site)*

The 3 quantitative criteria (CNR, E%, LBR) will be calculated by patient, for each contrast agent, in averaging the parameter for maximum 3 most representative lesions.

- Contrast to Noise ratio (CNR)

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

where SI_{lesion} = Signal intensity of lesion.
SI_{ht} = Signal intensity of healthy tissue (brain or spinal cord).
SD_{noise} = Standard Deviation (SD) of background noise.

- Percentage enhancement (E%) of lesion(s)

$$E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \text{x} 100$$

where SI_{post} = Signal intensity of lesion on post injection images.
SI_{pre} = Signal intensity of lesion on pre injection images.

- Lesion to Background Ratio (LBR) (pre and post)

$$\text{LBR} = \frac{SI_{lesion}}{SI_b}$$

where SI_{lesion} = Signal intensity of lesion.
SI_b = Signal intensity of background (healthy tissue in brain or spinal cord).

7.2.9 *Overall diagnostic preference (off-site read).*

The evaluation will be performed in a global matched-pairs fashion (images set 1b and 2b). For each randomized patient, all images (paired image set 1b or 2b) from the first MR examination, labeled as examination 1, will be displayed simultaneously with the corresponding paired images from the second MR examination, labeled as examination 2.

The assessment will be performed on all post-contrast T1-weighted images with 3-point scales:

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

IBRs 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 imaging eCRF)

7.2.10 *Safety profile of gadopiclenol and gadobutrol (on-site).*

The safety assessments will be followed up by evaluating results of vital signs, injection site tolerance, clinical laboratory parameters (blood samples) and adverse events (AEs) reporting.

- **Vital signs**

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

- Prior to each contrast agent injection (V2 is considered as baseline value)
- At 60 ± 15 minutes following each contrast agent injection
- One day after each contrast injection

Prior to the first injection, all clinically significant abnormal value might be reported in medical history section or AE section as per investigator's judgement. After the first contrast agent injection, all clinically significant abnormal value, as per investigator's judgement, will be recorded as AEs.

- **Injection-site tolerance**

For all patients, injection-site tolerance (pain, eruption, extravasation, inflammation, or other) will be assessed over 1 day following each contrast injection (during the injection, 60 ± 15 min 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 patient will be asked to specify the level of pain using a Numeric Pain intensity Scale (NPS [redacted]) from 0 (no pain) to 10 (maximal pain).

- **Local laboratory parameters**

Serum creatinine and eGFR will be obtained from local laboratory of each site prior MRI and one day post IMP injection. The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient.
According to ESUR guidelines: Post-contrast acute kidney injury (PC_AKI) is defined as an increase in serum creatinine of ≥ 0.3 mg/dL or of ≥ 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent.
For this trial, it is up to investigator to evaluate any change in serum creatinine within trial period as clinically significant or not; the investigator will report any clinically significant change as an AE..

- **Clinical laboratory parameters**

For each patient, blood samples will be performed from visit 2 to visit 5.
The following parameters will be obtained and assessed centrally:

- 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, Blood Urea Nitrogen (BUN) / urea, 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, Cystatin C.

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).

Prior to the first injection, all clinically significant abnormal value might be reported in medical history section or AE section as per investigator's judgement. After the first contrast agent injection, all clinically significant abnormal value, as per investigator's judgement, will be recorded as AEs.

- **Adverse events**

Adverse Events will be recorded throughout patient participation (see section 9.1.2).

8 TRIAL SCHEDULE AND PROCEDURES

The schedule of time and events to be performed is given in Table 1: Trial flow chart.

8.1 Trial Schedule

8.1.1 *Screening Visit – Visit 1 – Day (-7) to Day 0*

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

- Written informed consent will be obtained from the patient as described in Section 13.3;
- The patient will be attributed an Identification Number (see section 4.3);
- Checking of all eligibility criteria;
- Recording of demographic data (sex, race, ethnic data, height, age);
- Documentation of relevant medical history/current medical condition present before signing the informed consent including CNS disease justifying the MRI;
- Recording of patient intolerance history related to contrast agent: if previous intolerance to contrast agent, the type of the product should be collected;
- Documentation of previous CT/MRI or other imaging procedures documenting CNS lesion dated less than 12 months prior to ICF signature;
- Documentation of presence/absence of brain metastasis (in case of brain metastasis, the corresponding primary cancer will be recorded in medical history);
- 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;
- Review and recording 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 patient screening visit;
- First trial MRI visit and examination needs to be scheduled within 7 days (or can be performed on the same day if all the inclusion/non-inclusion criteria are met).

8.1.2 *Imaging/Randomization Visit – 1st MRI – Visit 2 – Day 0*

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

Procedures to be performed prior to MRI examination

- Checking of all the eligibility criteria;
- Any changes in concomitant treatments/procedures/therapeutic measures since the last visit will be documented;
- Measurement of vital signs (systolic and diastolic blood pressure (BP) and pulse Rate (PR)) and weight;
- A urine pregnancy test will be performed for female patient of childbearing potential and must be negative (test done at V1 will not be repeated at V2 if V1 done one day prior to V2. If V1 and V2 are done on the same day, one pregnancy test should be performed prior to patient randomization);
- Blood sample collection for local dosage of serum creatinine and evaluation of eGFR (results should be available prior to patient randomization to check eligibility criteria. eGFR value should be ≥ 30 mL/min/1.73 m^2 prior to the first MRI); The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient;
- Blood samples will be collected according to central laboratory manual;
- Assessment of AEs will be documented (see section 9);
- IWRS connection will be done to randomize the patient, to obtain the IMP box number, to calculate the volume of IMP to be administered based on the body weight and to record the date of the visit.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required sequences specified in Section 8.2.2).

The appropriate dose/volume of gadopiclenol and gadobutrol will be administered by IV as a bolus at the recommended rate of 2 mL/second using a power injector or manual injection in a peripheral vein of the antecubital region (recommended). IMP injection will be followed by a saline flush injection.

The following information will be documented in the source document and reported on clinical eCRF pages: date and time of contrast agent injection, location of injection site, actual volume administered (documentation of difference from theoretical volume), actual injection rate, overdose (if any), number of vials dispensed, number of IMP injected, injection method (power injector or manual), injection of saline flush (yes/no).

The start time of contrast injection will be recorded.

Procedures to be followed after MRI examination:

The patient will stay at the trial site for 60 ± 15minutes after the MRI examination is completed and the following procedures will be performed:

- Use/change of concomitant treatments during the visit will be documented;
- Vital signs (systolic and diastolic BP and PR) will be obtained 60 ± 15 minutes after the injection of contrast agent.
- Injection-site tolerance (pain, eruption, extravasation, inflammation, or other) will be assessed during the injection and 60 ± 15 minutes after the injection of contrast agent;

In case of pain, the patient will have to complete a Numeric Pain intensity Scale to indicate the pain intensity. Any sign of local intolerance will be reported as AE in the corresponding clinical eCRF page.

- Assessment of AEs will be documented (see section 9);
- Evaluation of the potential impact of contrast-enhanced MRI on patient treatment plan;
- 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.

8.1.3 *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/procedures/therapeutic measures will be documented;
- Blood sample collection for local dosage of serum creatinine and evaluation of eGFR. The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient;
- Blood samples will be collected according to central laboratory manual;
- Vital Signs (systolic and diastolic BP, PR) should be recorded;
- Injection-site tolerance is to be evaluated; In case of pain, the patient will have to complete a Numeric Pain intensity scale to indicate the pain intensity. Any sign of local intolerance will be reported as AE in the corresponding clinical eCRF page.
- Assessment of local serum creatinine results as per ESUR guidelines (see section 7.2.10)
- Assessment of AEs will be documented (see section 9);
- IWRS connection to record the trial visit;
- Remind the date of visit 4 to the patient.

8.1.4 *Imaging Visit – Visit 4– 2nd MRI – 2 days up to 14 days post V2*

Procedures to be performed prior to MRI examination

- Checking of non-inclusion criteria (see section 4.2);
- Measurement of vital signs (systolic and diastolic BP and PR) and weight;
- Any changes in concomitant treatments/procedures/therapeutic measures since the last visit will be documented;
- A urine pregnancy test for female patient of childbearing potential will be performed prior to the trial MRI and must be negative;
- Blood sample collection for serum creatinine dosage and verification that the local eGFR value is $\geq$ 30 mL/min/1.73 m^2. The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient;
- Assessment of local serum creatinine results as per ESUR guidelines (see section 7.2.10)
- Blood samples will be collected according to central laboratory manual;
- Assessment of AEs will be documented (see section 9);;

- IWRS connection will be done to obtain the IMPs box number, to calculate the volume of IMP to be administered based on the body weight and to record the date of the visit.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required sequences specified in Section 8.2.2).

The appropriate dose/volume of gadopiclenol and gadobutrol will be administered by IV as a bolus at the recommended rate of 2 mL/second using a power injector or manual injection in a peripheral vein of the antecubital region (recommended). IMP injection will be followed by a 0.9% saline flush injection.

The following information will be documented in the source document and reported on clinical eCRF pages: date and time of contrast agent injection, location of injection site, actual volume administered (documentation of difference from theoretical volume), actual injection rate, overdose (if any), number of vials dispensed, number of IMP injected, injection method (power injector or manual), injection of saline flush (yes/no).

The start time of contrast injection will be recorded.

Procedures to be followed after MRI examination:

The patient will stay at the trial site for 60 ± 15min after the MRI examination is completed and the following procedures will be performed:

- Use/change of concomitant treatments during the visit will be documented;
- Vital signs (systolic and diastolic BP and PR) will be obtained 60 ± 15 minutes after the injection of contrast agent.
- Injection-site tolerance (pain, eruption, extravasation, inflammation, or other) will be assessed during the injection and 60 ± 15 minutes after the injection of contrast agent; In case of pain, the patient will have to complete a Numeric Pain intensity Scale to indicate the pain intensity. Any sign of local intolerance will be reported as AE in the corresponding clinical eCRF page.
- Assessment of AEs will be documented (see section 9).
- Evaluation of the potential impact of contrast-enhanced MRI on patient treatment plan;
- Safety follow-up visit (Visit 5) needs to be scheduled 1 day post contrast agent injection;

8.1.5 *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/procedures/therapeutic measures will be documented;
- Blood sample collection for local dosage of serum creatinine and evaluation of eGFR. The same local methods of serum creatinine dosage and eGFR calculation should be used throughout the trial for a same patient;
- Assessment of local serum creatinine results as per ESUR guidelines (see section 7.2.9)
- Blood samples will be collected according to central laboratory manual;
- Vital Signs (systolic and diastolic BP, PR) should be recorded;
- Injection-site tolerance is to be evaluated; In case of pain, the patient will have to complete a Numeric pain intensity scale to indicate the pain intensity. Any sign of local intolerance will be reported as AE in the corresponding clinical eCRF page.

- Assessment of AEs will be documented (any AE not recovered should be followed up (see section 9.1.2);
- IWRS connection to record the trial visit;

During the course of the trial, if a patient is screen failed or is prematurely discontinued (see section 14.3.2), the new patient status should be recorded in the IWRS and in the clinical eCRF.

8.2 Imaging Characteristics

8.2.1 *Equipment*

The procedure will be performed using a MRI scanner that can perform the required pulse sequences. MRI units with 1.5T or 3T magnetic field will be used, regardless of the manufacturer. The following information must be recorded in the clinical eCRF: the manufacturer and field strength of the MRI device.

For a single patient, the same MR equipment for the two MRI examinations should be used.

8.2.2 *Imaging protocol*

The same parameter setting for the same sequence should be used for unenhanced images and for contrast-enhanced images in each patient.

The required sequences and parameters for gadopiclenol and gadobutrol per patient should be as similar as possible and as follows:

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

- Unenhanced :
  - 2D T1-weighted SE/TSE images
  - 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

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)

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.

Sequence parameters for brain and spine imaging will be provided in the Imaging Manual.

8.3 On-Site Reading of Images

For each investigational site, at least one experienced neuroradiologist or radiologist experienced in neuro-imaging will be appointed at the start of the trial to read all images of patients included at the site. Whenever possible, a second radiologist should be identified in each site and trained to the protocol in case the first radiologist is not available to read the images. The same radiologist should read, as far as possible, images from the same patient.

On-site image evaluations are image evaluations performed by blinded investigators involved in the conduct of the protocol or in the care of the patients.

8.4 Off-Site Reading of Images

Off-site images evaluations are image evaluations performed at sites that have not otherwise been involved in the conduct of the trial and by readers who have not had contact with patients, investigators, or other individuals involved in the trial.

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 patient or site identification. For all images, any sequence information will be removed. A complete audit trail of any changes to the file headers will be maintained.

The blinded image evaluations will be performed by independent blinded radiologists (3 independent blinded radiologists will evaluate primary criteria, 3 independent blinded radiologists will be involved to assess images on the global pairs fashion and 1 radiologist will perform lesion tracking). An imaging 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 trial purpose are documented by the independent blinded readers.

8.4.1 *Manuals and Supplies*

Guerbet (or its Imaging Core Laboratory) will document the imaging tasks and obligations of the investigational site in an Imaging Manual. As defined in Section 8.2.2, the standardized image acquisition guidelines or imaging protocol will be provided to the sites as part of the Imaging Manual.

In addition, the Imaging Manual will detail the steps required for masking confidential patient information and transferring images to the Imaging Core Laboratory.

Guerbet (or the Imaging Core Laboratory) will document the central imaging process in a Blinded Imaging Evaluation Charter.

8.4.2 *Site Qualification*

Guerbet's agent (CRO, Imaging Core Laboratory or monitors) will perform pre-trial site selection. This contact will allow ensuring that the imaging protocol can be performed by the site, is programmed and prepared prior to enrolment of the first patient and that the Imaging Manual will be accurately followed by the investigator.

8.4.3 *Receipt and Tracking of Images*

Guerbet (or its 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 trial start. Images will be tracked in the database of the Imaging Core Laboratory.

8.4.4 *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. Patient 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 images parameters with the imaging protocol, poor quality images), the investigational site will be notified concerning 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 training for investigator sites with recurring image quality issues.

8.4.5 *Independent Blinded Readers Training*

A panel of independent, board-certified readers, with expertise in the interpretation of CNS images with no participation in the trial and no affiliation with any institution where the trial will be conducted, will be selected for the off-site reading.

All independent readers will be trained to the trial and reading specifications. Before the readers start the readings, they will have to successfully complete training sessions (refer to “Blinded Image Evaluation Charter” for details).

Independent readers are readers that are completely unaware of findings of other readers (including findings of other blinded readers and on-site investigators) and are readers who are not otherwise influenced by the findings of other readers.

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.

8.4.6 *Image Randomization*

When a sufficient number of images are available for readings, a batch of images will be presented to the blinded readers.

The patients within each batch will be ordered at random without stratification into groups of patients.

Various modalities of images from the same patient 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 (Pre & Paired images) and between two MR examinations for the same patient, to minimize recall bias.

8.4.7 *Blinded Assessment of Images*

Imaging database including all evaluable images will be assessed by the independent readers. The reading will be performed in a strictly fully blinded manner.

No communication on patient specific image findings will be allowed between the independent 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).

8.4.8 *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 trial patients since each patient will be read by 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 50 cases are reviewed and no sooner than two weeks from the original reviews of these patients. 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.

8.4.9 *Lesion tracking/Matching*

A concordance reading process (lesion tracking) will be performed as an independent off-site procedure. The purpose is to guarantee an unambiguous assignment (matching) of the lesions between modalities (Pre and Paired images) of the same MR examination between two MR examinations for the same patient, and between readers. Lesion tracking will be carried out by another independent radiologist (so-called concordance reader) in blinding condition (except the ID number of lesions) on the basis of the off-site readers' assessments. Once the concordance process is done, correspondence/tracking lesion tables should be obtained, so that lesions could be compared for analysis within readers or for the inter- and intra-reader (refer to trial "Blinded Image Evaluation Charter" for details).

8.4.10 *Image Archive 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 trial. Measurements will also be stored so that these data may be audited if necessary. A copy of images transferred by the investigators to Imaging Core Laboratory will be transferred to Guerbet after database lock for archiving.

8.5 Non Imaging Central procedures: central laboratory

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

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, Blood Urea Nitrogen (BUN) / urea, 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, Cystatin C.

All laboratory reports must be promptly reviewed by the Investigator who will initial and date upon review. Change(s) in post-dose test values considered clinically significant, which would require either additional control or therapy, must be documented in the patient's source document. All post-injection values considered clinically significant by the investigator will be reported as AEs and followed until recovery or stabilization of the values if irreversible (sequelae).
Central laboratory results obtained at V2 prior to IMP injection should be assessed by the investigator as clinically significant or not and reported in medical history section or AE section as per investigator judgement.

Samples obtained in this trial will not be retained or used for any other purposes.

Name and address of the central laboratory will be detailed in the central laboratory manual.

9 SAFETY REPORTING

The Investigator will report to Guerbet any adverse event whether related or not to the investigational medicinal product, serious or not, that occurred in a trial patient during its participation to the trial according to the below instructions. Special situations such as medication errors, misuses, suspicion of transmission of an infectious agent via an IMP, unusual failure in efficacy, overdose (symptomatic or not), drug exposure during pregnancy or breastfeeding even if uneventful, suspected drug-drug interaction with another product (symptomatic or not) will also be reported to Guerbet.

The definition, modalities of collection and reporting are provided below.

9.1 Adverse Event

9.1.1 *Definition of Adverse Event*

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be:

- any unfavorable and unintended sign, including an abnormal finding from an additional examination (lab tests, X-ray, ECG…) deemed clinically significant by the investigator;
- any symptom or intercurrent disease;
- any worsening during the trial of a symptom or a disease already present when the patient entered the trial (increase in frequency and/or intensity).

(Note: for US participating sites only: for Guerbet sponsored clinical studies, the term adverse events will be used (as opposed to adverse drug experience)).

Any disease identified and diagnosed by trial imaging examination with contrast agent will not be considered as AE. It may be collected in clinical eCRF as medical history or trial disease.

The patient's disease under investigation and part of inclusion criteria or any pre-existing disease is not reported as AE, nevertheless, any worsening of such pathologies during the course of the trial has to be considered as an AE.

9.1.2 *Collection and recording of Adverse Events*

The Investigator or his/her designee will invite the patient to report any experienced abnormality as part of the usual clinical follow-up. In addition, any abnormal finding assessed as clinically significant in the context of the trial by the Investigator (see section 9.1.1) should be considered as AE and reported in the AE section of the clinical eCRF.

All AEs, whether considered as related or not to the IMP and/or any protocol procedures including imaging procedures, and whether serious or not, should be reported and documented in the medical file and the appropriate section of the clinical eCRF according to the Table 5.

Table 5: Collection and reporting of AEs throughout and after the trial

Periods and types of AEs to be reported	**Screening**	**From randomization to last follow-up visit**	**After end of participation**
Not related non-serious AEs	X*	X	
Not related SAEs	X	X	
Adverse Event of Special Interest (AESI)	X	X	
Related[$] AEs (serious or not)	X	X	X
Pregnancy cases	NA	X	X**

[$] related to the IMP and/or any protocol procedures including imaging procedures

* The events which occur before the first IMP administration, and which are not serious and not related to the trial procedures, might be recorded as medical history upon the investigator's judgement.

** see the period of collection described in section 9.3.2

As reminder the patient's participation is defined as the period from the screening visit (ICF signature) to the last trial visit in the general case and defined in section 10 in case of premature discontinuation.

Any AE is followed-up from its onset to recovery or stabilization of sequelae. If no follow-up is performed, the investigator must provide a justification in the medical file and eCRF.

9.1.3 *Description of Adverse Events*

The following guidelines and definitions should be used by the investigator for the description of an AE when reporting information in clinical eCRF and any specific AE report forms:

- **Nature (diagnosis) 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 clinical eCRF.
- **Date and time of onset:** date and clock time of the AE start.
- **Intensity:**
  - Mild: the patient 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 patient or it is of some clinical consequence
  - Severe: the patient 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)**:** This date is the date when the event has come to its ends or to its initial intensity (for the events that had been an aggravation of a pre-existing disorder). If the AE is still ongoing by the time of end of trial follow-up for the patient (i.e. last trial visit), the patient 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 IMP:**

- Related: the definition of adverse reaction (AR) 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 trial drug and the event, but an obvious alternative cause exists (e.g. the patient's underlying medical condition or concomitant therapy).

- **Causal relationship to a trial procedure (blood test, imaging procedure itself etc…):**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the procedure. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no procedure was performed yet or when no causal relationship exists between the trial procedure and the event, but an obvious alternative cause exists (e.g. the patient's underlying medical condition or concomitant therapy).
- **Outcome:**
  - Recovered/resolved: the AE is no longer present at any intensity or return to baseline intensity (for pre-existing disorders) or values for biological data.
  - Recovered/resolved with sequelae: the AE is resolved but residual effects are still present (to be specified on the AE form).
  - Not recovered/not resolved: the AE is still present at the last contact with the patient.
  - Fatal: this AE caused or directly contributed to the patient's death.
- **Action taken with regard to administration of the IMP:**
  - No action: for AE occurring during the pre-treatment/procedure after the post-treatment/procedure period, or if the IMP dosing/administration would not change in spite of the occurrence of the AE.
  - IMP interrupted: the IMP administration is interrupted (e. g. extravasation…) or the patient is withdrawn from any other IMP administration planned during the trial but without known contra-indication to the drug.
  - IMP definitively discontinued: the event leads to a definite contra-indication to the drug (e.g. confirmed hypersensitivity…).
  - IMP unblinding.
- **Other action taken:**
  - AE-targeted medication: the patient took a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the clinical eCRF ("concomitant medication" section).
  - Other AE-targeted action: therapeutic measures other than corrective drug administration (e.g. ice, heating pad, brace, cast…) or patient underwent a procedure (surgery, physiotherapy, additional laboratory test…) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the clinical eCRF ("procedures/therapeutic measures" section).
  - Trial discontinuation: the AE leads to patient discontinuation from the trial.

- **Adverse event of special interest (AESI)** should be indicated (see section 9.3.3 for AESI definition)
- **Assessment of the seriousness of the AE**: see Section 9.2 for SAE definition.

9.2 Serious Adverse Event

9.2.1 *Definition of Serious Adverse Event*

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose (ICH E2A):

- Results in death
- Is life-threatening
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect
- Is an important medical event

- Important medical event: medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
- Life-threatening in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Hospitalization refers to an admission and overnight stay at the hospital due to the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

In case of a SAE, the investigator is responsible for the measures to be taken to ensure the safety of the trial patients.

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

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

- Any hospitalization that had been planned before the trial and that will take place during the trial, provided there is no aggravation of the disease to which it is related.
- Hospitalizations, which are not associated to an adverse event (such as hospitalization for check-up).

No anticipated SAE is defined in this protocol as patient population under trial is suffering from CNS lesions but not from a specific pathology therefore no anticipated SAE has been identified.

9.2.2 *Reporting Serious Adverse Events (SAE)*

All SAEs **must be reported immediately** by the investigator to Guerbet. Therefore, the investigator must immediately forward to Guerbet Pharmacovigilance department a duly completed report form for SAE, AESI or pregnancy [redacted] provided by Guerbet with trial documents, even if it is obvious that more data will be needed in order to draw any conclusion:

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

In case of emergency, Guerbet Pharmacovigilance department may be contacted at:

+ 33 (0)1 45 91 50 00.

SAEs, occurring at any time during the patient's participation to the trial have to be reported also in medical file and in the appropriate section of the clinical eCRF (see Section 9.1.2)

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

- Patient's details including age, sex and patient's trial identification number,
- Patient'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 of 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 initial notification),
- Date and time of investigational drug administration,
- Seriousness criterion,
- Causal relationship to the investigational drug or procedure (mandatory),
- Outcome at the time of reporting.

If the investigator is aware of any new relevant information concerning a SAE (e.g.: outcome or any information that can have an impact on the assessment of the seriousness or the causal relationship between the SAE and the IMP), he has to send immediately to Guerbet Pharmacovigilance department the report form for SAE, AESI or pregnancy duly completed [redacted].

In order to comply with current regulations as well as for comprehensive assessment purposes, additional information (e.g. autopsy results, biological values…) or clarifications may be required by Guerbet in a timely fashion to ensure accurate follow-up and assessment of each case and should be transmitted, anonymized, with a specific form [redacted] as soon as they are available.

SAEs should be followed up by the investigators until complete recovery of the patient or, if not possible, until stabilization of sequelae.

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

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

The transmission of the information to Guerbet does not release the investigator from his responsibility to inform the regulatory authorities and or IEC/IRB, if applicable.

No anticipated SAE has been identified in this trial therefore no modalities of collection and reporting are described.

9.3 Special situations

9.3.1 Cases of overdose, lack of efficacy, interaction with drug or device, medication errors or misuses

The safety information regarding the following special situations has to be collected and reported by the investigator with the same procedure as for AE, even if uneventful:

- Medication error: an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (e.g.: wrong route of administration). A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures,
- Misuse: where the medicinal product is intentionally and inappropriately used not in accordance with the protocol,
- Occupational exposure to an IMP: an exposure to a medicinal product as a result of one's professional or non-professional occupation,
- Suspected drug-drug or drug device interaction with another product.
- Unusual Lack of efficacy: for Guerbet imaging products, lack of efficacy is mainly represented by cases of "lack of contrast" or " poor iconographic quality " or "no contrast" or "poor contrast" etc. for MRI examination.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose, which is 0.3 mmol/kg for the gadopiclenol and above 1.5 mmol/kg, or less according to local reference document (SmPC), for gadobutrol.

9.3.2 Pregnancy

Any participating patient who becomes pregnant or, for a male patient/is aware of the pregnancy of his partner during the trial participation should inform immediately the investigational site. The female patient should immediately withdraw from the trial and must not receive any IMP.

Any pregnancy (with or without an Adverse Event) of a woman participating in the trial or of a partner of a man participating in the trial that is discovered after the ICF signature must be reported to Guerbet Pharmacovigilance *via* the report form for SAE, AESI or pregnancy [redacted] (see section 9.2.2) unless the conception date is over one week (for GBCAs) after the last IMP administration. In this case, there is no need to report the pregnancy to Guerbet except in case of noxious effect related to the trial drug according to investigator's opinion.

A specific signed ICF should be obtained before collection of information if the pregnant woman is the partner of a trial patient.

Pregnancy will be monitored until delivery (health of infant up to 8 weeks of age) or early termination.

Specific forms [redacted] will be provided to the investigational sites by Guerbet Pharmacovigilance department. These forms will be used to collect information on the medical history of the pregnant woman and any risk factor of pregnancy complication, and on the follow-up and outcome of the pregnancy.

Any complication of pregnancy will be reported as an AE or SAE, as appropriate.

9.3.3 Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI), serious or non-serious, is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

For Guerbet, the transmission of an AESI to the Guerbet Pharmacovigilance Department respects the same time frame as an SAE and should be reported using the report form for SAE, AESI or pregnancy [redacted].

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

9.3.4 Any suspicion of transmission of an infectious agent via an IMP

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

9.4 Other important safety issue / new fact

Any new data which may lead to a reassessment of the benefits / risks balance of the research or product being studied, changes in the use of that product, the conduct of the research or documents relating to the trial or to suspend or interrupt or modify the protocol of the trial or similar searches have to be evaluated by Guerbet.

It may include any new event likely to affect the safety of the patient's and that may be related to the conduct of the trial or the development of the trial drug such as:

- A SAE which could lead to the modification of the conduct of the trial (ex: SAE associated with the trial procedures, SUSAR).
- A new major finding from an animal study,
- A temporary halt of a trial for safety reasons if the trial is conducted with the same IMP in another country by the same sponsor,
- Recommendations of the safety committee if any, where relevant for the safety of patients,
- Increase in the frequency of an expected event considered as clinically significant.

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

Consequently, this type of important safety issue might lead also to:

- Urgent safety measures and their notification
- Substantial trial documents modifications
- Premature discontinuation of the trial
- Premature discontinuation of the patient

The Reference Safety Information (RSI) used for the assessment of expectedness of serious adverse reactions is the investigator brochure in force for gadopiclenol and the SmPC for gadobutrol.

9.5 Unblinding Procedures

The investigator may, under exceptional circumstances unblind the individual trial treatment group if he/she considers that this procedure is relevant to the safety of the trial patient. Individual trial treatment unblinding is described in Section 5.3.3. Information that unblinding has been performed by the investigator must be documented in the patient medical file, in the clinical eCRF and in the report form for SAE, AESI or pregnancy 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 blinded personnel responsible for trial management, data analysis, and interpretation of results at the trial's conclusion.

10 SCREEN FAILURE AND PREMATURE DISCONTINUATION

10.1 Screen failure

Screen failed patients are defined as patients who consent to participate in the clinical trial but are not subsequently randomized. For this trial, a patient who has signed ICF cannot be re-screened.
Data collected for screen failure patients, refer to section 14.3.2.

10.2 Premature Discontinuation of the trial per Guerbet Decision

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

Guerbet will inform the relevant authorities in each country, the ethics committees, the trial site investigators, pharmacists and hospital authorities according to the regulatory texts in force.

10.3 Premature discontinuation

Premature discontinued patients are defined as patients who consent to participate in the clinical trial and are discontinued from the trial after randomization
Data collected for premature discontinued patients: Please refer to section 14.3.2.

10.4 Reasons for patient's screening failure and premature discontinuation

Criteria for screen failure and premature discontinuation of patients:

- Inclusion criteria not met /Non-inclusion criteria met
- Adverse Event (according to the investigator's judgement);
- Adverse Event of Special Interest (AESI);
- Withdrawal of patient's consent:
    - If the patient withdraws consent for disclosure of future information, Guerbet may retain and continue to use any data collected before such a withdrawal of consent.
    - If a patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site's records.
- Patient lost to follow-up (date of last contact will be documented in the medical file and the clinical 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 patient's medical file;
- Discovery of an unexpected, significant, or unacceptable risk to a patient enrolled in the trial;
- At the discretion of the investigator if the patient safety or well-being is not compatible with trial continuation;
- Other reason (to be specified)

10.5 Enrolment of additional patient

Patients prematurely discontinuing the trial will not be replaced.

In the event of premature discontinuation, patients will receive adequate follow-up from on-site investigators.

11 STATISTICAL CONSIDERATIONS

The following sections summarize the statistical considerations, which are fully described in the Statistical Analysis Plan.

11.1 Statistical Method

Primary objective 1: superiority of Paired images versus Pre images of gadopiclenol MR examination regarding lesion visualization co-primary criteria

The null hypothesis is that the difference in mean scores between Paired images and Pre images for each of the 3 primary criteria is equal to 0.
The alternative hypothesis is that the difference in mean scores between Paired images and Pre images for each of the 3 primary criteria is greater than 0.

A paired t-test is performed at a one-sided 2.5% significance level for each co-primary criteria.

All co-primary criteria are considered as following a standard normal distribution. Normality will be checked by means of plots.

To conclude that gadopiclenol-enhanced MRI is superior to unenhanced MRI, the null hypothesis has to be rejected for all co-criteria simultaneously hence the overall Type I error rate does not need to be adjusted.

Primary objective 2: non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria

The null hypothesis is that the difference in mean scores between gadopiclenol and gadobutrol for each of the 3 primary criteria is equal to the non-inferiority margin.

The alternative hypothesis is that the difference in mean scores between gadopiclenol and gadobutrol for each of the 3 primary criteria is greater than the non-inferiority margin.

Student's t-based two-sided 95% confidence interval (95%CI) of the gadopiclenol-gadobutrol difference will be calculated for each co-primary criteria and compared to the non-inferiority margin.

All co-primary criteria are considered as following a standard normal distribution. Normality will be checked by means of plots.

To conclude that gadopiclenol is non inferior than gadobutrol, the null hypothesis has to be rejected for all co-criteria simultaneously hence the overall Type I error rate does not need to be adjusted.

Further, after the non-inferiority is demonstrated, the superiority of gadopiclenol over gadobutrol will be tested using the same method. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

For FDA, the primary objective 1 is to be achieved.

For EMA, both primary objectives 1 and 2 are to be achieved

11.2 Sample Size

Number of patients for the primary objective 1:

Expecting that for each co-primary criteria, the difference in mean scores will be 0.35 (["Paired" – "Pre"] within patient mean of lesion scores) with 1.5 standard deviation, a sample of 200 patients in the gadopiclenol group will have 90% power when using a single group superiority t-test with a 0.025 one-sided significance level.
As a 20% drop-out rate is expected, sample size increases to 250 patients with CNS lesions.

The success hypothesis used in the sample calculation ("Paired" lesion score mean is at least 0.35 higher than "Pre" lesion score mean) is based upon the Gutierrez publication [10] where the minimal observed difference mean was 0.41 with a SD ranging from 0.5 to 0.8.

Mean (SD) of the difference between combined unenhanced and gadobutrol-enhanced imaging vs unenhanced imaging (N = 336).

Reader	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	0.67 (0.66)	0.62 (0.47)	1.26 (0.61)
2	0.72 (0.78)	0.82 (0.61)	1.59 (0.77)
3	0.43 (0.50)	0.41 (0.52)	1.06 (0.51)

Considering that in the current trial the scale used is not exactly the same (4-point scale instead of 3-point scale for one parameter) and to account a possible greater heterogeneity, the difference is set to 0.35 with 1.5 standard deviation.

Number of patients for the primary objective 2:

- Non-inferiority margin:

For EMA, both primary objectives 1 and 2 are to be achieved therefore this trial will provide a direct demonstration of the superiority of gadopiclenol images over unenhanced images (objective 1). So, it can be considered as three-armed trial design with unenhanced images as placebo as described in *EMA guideline on the choice of the non-inferiority margin* [11]. As such, it is not necessary to define a value for non-inferiority margin to establish that gadopiclenol has efficacy over unenhanced images.

A 10% non-inferiority margin was considered clinically as an unimportant difference and therefore relevant to establish acceptable efficacy relative to gadobutrol (objective 2). Based on the Guerbet Phase IIb GDX-44-004 clinical trial results of lesion visualization criteria, the mean score for each of the 3 co-criteria is expected to be equal to 3.5, so the margin is set to 0.35 (10%).

- Sample size hypothesis:

The standard deviation on lesion visualization criteria for gadopiclenol is estimated on the basis of the Guerbet Phase IIb GDX-44-004 clinical trial results on lesion visualization criteria presented in the table below.

Mean (SD) of the combined unenhanced and gadopiclenol-enhanced imaging (N = 61).

Reader	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	3.37 (0.55)	3.34 (0.64)	3.23 (0.80)
2	1.97 (0.74)	1.71 (0.75)	3.76 (0.58)
3	3.72 (0.49)	3.72 (0.49)	3.68 (0.50)

Considering that the results for gadobutrol would be similar (meaning that the standard deviation of the difference is expected ranging from $\sqrt{2}$*0.50=0.7 to $\sqrt{2}$*0.80=1.15) and taking into account a possible greater heterogeneity of patient population to be included in the trial, the expected standard deviation of difference between gadopiclenol and gadobutrol is estimated to 1.75.

For this 2x2 cross-over design, the statistical analysis is based on the observed Student's t-based two-sided 95% confidence interval (95%CI) of the gadopiclenol-gadobutrol difference for each co-primary criteria. An enrollment of 200 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin set to 0.35. Assuming 80% power and for each co-primary criteria, the expected difference in mean scores is 0 with an expected standard deviation of 1.75.

If one assumed a patient drop-out rate of 20%, a minimum enrollment of 250 patients with CNS lesions is planned.
Therefore, a total number of 250 patients will allow a sufficient power to meet both primary objectives.

11.3 Planned Analysis

11.3.1 *Disposition of patients*

Number of patients undergoing each visit will be presented by series (gadopiclenol-gadobutrol / gadobutrol- gadopiclenol) and overall.

The overall disposition will be presented by series and overall. The reason of screen failure will be presented overall and the reason of premature discontinuation will be presented by series and overall. (see section 10 for screen failure and premature discontinuation definition).

Number of patients by site will be presented overall as well.

11.3.2 *Data Sets Analyzed*

The patient sets for this trial are defined below:

- The Screened patients Set (SPS) will include all patients having signed the inform consent form
- The Safety Set (SS) will include all patients having received at least one injection of IMP regardless of the quantity
- The Full Analysis Set 1 (FAS1) will include all patients who have a valid primary criterion assessment
    - FAS1 will include all patients who have both gadopiclenol pre and paired images assessable (for primary objective 1)
    - FAS2 will include all patients who have both gadopiclenol and gadobutrol paired images assessable (for primary objective 2)
- The Per-Protocol Set (PPS): will include all patients who have no major protocol deviations and a valid primary criterion assessment.
    - PPS1 will include all patients from the FAS1 who have no major protocol deviations for primary criteria 1
    - PPS2 will include all patients from the FAS2 who have no major protocol deviations for primary criteria 2

11.3.3 *Protocol Deviations*

As per International Conference on Harmonization (ICH) E3 guideline, a protocol deviation is any change, divergence or departure from the trial design or procedures defined in the protocol, with or without impact to the patient safety or the efficacy assessments.

Protocol deviations will be gathered from monitoring files, clinical database and external vendors of off-site data (imaging, laboratory data…).

Protocol deviations will be split in major and non-major deviations. A major deviation is defined as a deviation having an impact on the primary criterion.

Examples of protocol deviations to be stated as major are following:

- Patient not presenting, at the time of inclusion, with known or highly suspected focal areas of disrupted Blood Brain Barrier
- Imaging protocol not respected with major impact on primary criterion
- Informed consent not signed
- IMP not injected

Other major deviations can be specified during the course of the trial and the exhaustive list of major and non-major deviations will be provided in the statistical analysis plan.

Major and non-major deviations will be presented apart by series and overall.

11.3.4 *Demographics and Baseline Characteristics*

Demographic parameters are age, sex, race, ethnic origin, childbearing potential, body weight, height, and body mass index (BMI). Baseline characteristics are the patient'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 sex, patient’s history characteristics and concomitant treatments.
Patient's medical history will be coded using the MedDRA dictionary and tabulated by body system, preferred term and status (concomitant or not).
Patient's concomitant treatments will be coded using the Anatomical Therapeutic Chemical (ATC) Drug dictionary and tabulated by ATC code.

Demographics and baseline characteristics will be displayed by series and overall.

11.3.5 *Compliance*

The number of patients with actual volume of trial product different from the theoretical one will be presented by contrast agent group (gadopiclenol and gadobutrol).

The absolute (mL) and relative (%) differences between theoretical and actual volumes of trial product will be presented by contrast agent group.

11.3.6 *Efficacy Analysis*

Primary analysis

Superiority of Paired images versus Pre images of gadopiclenol MR examination regarding lesion visualization co-primary criteria (for objective 1)

For gadopiclenol, the difference “Paired” -”Pre” for each of 3 co-primary criteria 1 will be analyzed using paired t-tests using the FAS1. Results will be presented per reader.

To be successful, 2 out of 3 readers will have to meet the alternative hypothesis for the 3 co-primary criteria in the gadopiclenol group: a statistically significant (one-sided p≥0.025) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions.

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria (for objective 2)

The Student's t-based two-sided 95% confidence intervals of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 co-primary criteria 2 using the PPS2. If the lower bound of this confidence interval is above the non-inferiority margin set to 0.35 for at least 2 out of 3 readers and for the 3 co-primary criteria simultaneously, then non-inferiority between gadopiclenol and gadobutrol will be concluded.

As soon as the non-inferiority is demonstrated, the superiority of the gadopiclenol over gadobutrol will be tested using the same method and using the FAS2 and PPS2. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

Secondary analyses

Additional analysis of the co-primary criteria

Supportive analyses of the non-inferiority analysis
The non-inferiority analysis will be repeated using the FAS2.

Assay sensitivity:
For gadobutrol, the difference "Paired" -"Pre" for each of 3 co-primary criteria will be analyzed using the same analysis as described for superiority on the FAS2. Results will be presented per off-site reader.

Intra-reader variability
Intra-reader variability will be analyzed in a subgroup of 10% of patients randomly selected for whom the off-site readers have re-read the images.

Intra-reader variability will be studied by a Bland-Altman graph. Descriptive statistics and the Intra-Class Correlation (ICC) will also be provided.

The analyses will be performed using the FAS1 and FAS2.

Inter- reader variability
Inter-reader variability will be evaluated on the whole set of trial patients, since each case was read by 3 different readers.

The same methodology as the one presented above for intra-reader variability will be applied.

The analyses will be performed using the FAS1 and FAS2.

Secondary criteria analyses
All analyses of the secondary criteria will be done using the FAS1 for analyses by MRI modalities, and FAS2 for analyses by contrast agent groups, except otherwise specified.

Lesion visualization (on site)
Same analysis as off-site lesion visualization criteria will be carried out for on-site evaluation

Improvement in lesion visualization scores at patient-level, paired versus pre images.

Improvement in lesion visualization at patient-level will be tabulated by contrast agent groups; off-site and on-site reader's outcomes will be separately analyzed.

Technical adequacy of images
Technical adequacy and assessable status of images will be tabulated by MRI modalities and contrast agent groups; off-site and on-site reader's outcomes will be separately analyzed.
Number of lesions
The number of lesions per patient will be tabulated by MRI modalities and contrast agent groups; MRI modalities ("Paired" vs. "pre") and contrast agent groups (gadopiclenol vs. gadobutrol) will be compared with a multivariate model using the negative binomial distribution. Off-site and on-site reader's outcomes will be separately analyzed.

Size of lesions
The size of the 3 largest representative lesions per patient will be assessed by off-site readers and on-site radiologists and will be summarized by MRI modalities and contrast agent groups; off-site and on-site reader's outcomes will be separately analyzed.

Location of lesions
The localization of the 3 largest representative lesions by patient will be assessed by off-site readers and on–site radiologists and will be displayed by MRI modalities and contrast agent groups; 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 will be displayed by MRI modalities and by contrast agent groups; off-site and on-site reader's outcomes will be separately analyzed.
Diagnostic confidence will be tabulated by contrast agent groups; off-site and on-site reader's outcomes will be separately analyzed.

Impact of contrast-enhanced MRI on patient treatment plan:
The impact on patient treatment plan will be assessed by on-site radiologists and will be tabulated by contrast agent groups.

Contrast to Noise Ratio (CNR)
CNR is calculated from the Signal Intensity (SI) measurement of maximum 3 representative lesions by the 3 independent off-site readers (see section 7.2.8)

For each reader, CNR will be tabulated by contrast agent groups and differences between contrast agents will be tested using a Student's t-test.

Percentage Enhancement (E%) of lesion(s)
E% is calculated from the Signal Intensity (SI) measurement of maximum 3 representative lesions by the 3 independent off-site readers (see section 7.2.8)

For each reader, E% will be tabulated by contrast agent groups and differences between contrast agents will be tested using a Student's t-test.

Lesion to Background Ratio (LBR)
LBR is calculated from the Signal Intensity (SI) measurement of maximum 3 representative lesions by the 3 independent off-site readers (see section 7.2.8)

For each reader, LBR will be tabulated by contrast agent groups and differences between contrast agents will be tested using a Student's t-test.

Overall diagnostic preference
For each off-site reader, the overall diagnostic preference will be tabulated and gadopiclenol will be compared to gadobutrol by a Wilcoxon signed-rank test.

The reason of this preference will be displayed according to the contrast media preferred.

11.3.7 *Adverse Event*

An overall summary of AEs will be presented using the Screened Patient Set (SPS) to catch AEs of patients who did not receive trial drug. The table will be presented overall, only with the following variables:

- Total number of AEs.
- Total number of patients with at least one AE.
- Distribution of the number of AEs reported by patients (0, 1, 2 or 3 or more AEs).
- Total number of Serious AEs (SAEs) according to the seriousness criteria.
- Total number of patients with at least one SAE according to the seriousness criteria.
- Total number of AESIs.
- Total number of patients with at least one AESI.
- Total number of AEs according to intensity (severity).
- Total number of patients with at least one AE according to intensity (severity)
- Total number of AEs according to the outcome.
- Total number of patients with at least one AE according to the outcome.
- Total number of AEs requiring a concomitant drug (other action taken)/procedure.
- Total number of patients with at least one AE requiring a concomitant drug/ therapeutic measures (other action taken)/procedure.
- Total number of AEs leading to premature discontinuation.
- Total number of patients with at least one AE leading to premature discontinuation.
- Total number of AEs with causal relationship to the procedure.
- Total number of patients with causal relationship to the procedure.

The same overall summary will be displayed by contrast agent group for Treatment Emergent AEs (TEAEs) using the Safety Set. The following variables will be also presented:

- Total number of TEAEs with causal relationship to the IMP.
- Total number of patients with at least one TEAE with causal relationship to the IMP.
- Total number of TEAEs requiring interruption of IMP.
- Total number of patients with at least one TEAE requiring withdrawal of IMP.

The number and percentage of patients with at least one TEAE will be presented using the Safety Set by contrast agent group according to Primary SOC and PT.

The number and percentage of patients with at least one TEAE with causal relationship to the IMP will be presented using the Safety Set by contrast agent group according to Primary SOC and PT.

The number and percentage of patients with at least one AESI will be presented using the Safety Set by contrast agent group according to Primary SOC and PT.

The number and percentage of patients with at least one AESI with causal relationship to the IMP will be presented using the Safety Set by contrast agent group according to Primary SOC and PT.

11.3.8 *Laboratory data*

Laboratory data analysis will be done using the Safety Set.

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 by contrast agent group. 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.

11.3.9 *Other safety observations*

Other safety observations analysis will be done using the Safety Set.

Extent of exposure
Duration between ICF signature, IMP administrations and end of trial will be tabulated by contrast agent group.
Volume actually administered and, actual rate of administration, will be tabulated by contrast agent group.

Injection site tolerance
Number of patients experiencing pain, eruption, extravasation and inflammation at site injection will be tabulated by contrast agent group. Pain at injection site will be measured using the Numeric Pain intensity Scale (NPS) and NPS measurements for these patients will be tabulated by contrast agent group.

Vital signs
Vital signs will be analyzed quantitatively and qualitatively by contrast agent. Qualitative analyses will be done via comparison of vital signs data to their normal ranges (see section 7.2.10) and according to their clinically significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

11.4 Specific Statistical Analytical considerations

11.4.1 Adjustments for Covariates

As no factor has been identified as having a large impact on the primary and secondary criteria of analysis, no covariates are added in the efficacy models.

11.4.2 Handling of Dropouts or Missing Data

No imputation will be performed in this trial.

11.4.3 *Interim Analyses*

No interim analysis is planned.

11.4.4 *Multicenter Trial*

As a high number of sites is expected for this trial, the site factor will not be included in the models for efficacy. The number of patients included in each site will be displayed in a disposition table.

11.4.5 *Multiple Comparisons/Multiplicity*

For FDA, the primary objective 1 is to be achieved. The primary objective 2 will serve as one of the secondary objectives.

For EMA, both primary objectives 1 and 2 are to be achieved

Therefore, no multiplicity adjustment is needed for this trial as only one objective should be reached for FDA and the two primary objectives should be reached simultaneously for EMA.

Furthermore, each objective (superiority of Paired vs Pre, and non-inferiority of the two contrast agents), will be considered achieved only if the null hypothesis is rejected for the 3 co-primary criteria simultaneously for at least two readers out of three. Each reader will be analyzed separately.

11.4.6 *Use of an "Efficacy Subset" of patients*

As the primary objective 1 is superiority, the corresponding analysis will be done using the Full Analysis Set and then the analysis repeated using the Per Protocol Set.

As the primary objective 2 is non-inferiority, the corresponding analysis will be done using the Per Protocol Set and then the analysis will be repeated using the Full Analysis Set.

11.4.7 *Examination of Subgroups*

No examination of subgroups is planned.

12 TRIAL COMMITTEES

Based on safety related to non-specific macrocyclic GBCAs and results of gadopiclenol phase I to IIb trial, no committee will be set up for this trial.

The overall gadopiclenol safety (based on consolidated available data from all gadopiclenol clinical studies) will be evaluated and followed up by an internal Guerbet safety committee, therefore no specific trial committee will be set up.

The Guerbet Safety Committee whom core members are the European Qualified Person responsible for Pharmacovigilance (EU-QPPV), the Development, Medical and Regulatory Affairs Director, the Global Head of Regulatory Affairs who is also the Head of Preclinical Development including additional members such as medical expert and pharmacovigilance expert reviews gadopiclenol Integrated and compiled data (e.g. Initial Signal Report) every 3 months.

The Safety Committee decisions may have an impact on other documents (e.g. clinical studies documents, etc.). The appropriate actions are taken accordingly.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 References

The trial/ 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: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 19 November 2016
- 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
- Regulation (EU) 2016/679 Of The European Parliament And Of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- 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 and other specific populations regulations

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

As per international regulation, the clinical trial may be initiated only after having received the approval by and Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the authorization by the national Regulatory/Competent Authority. The final written approval and authorization must be available for a given investigational site when initiating the trial conduct at this particular site. Amongst all documents required locally, the approval and authorization must be obtained for the protocol, investigator's brochure, the patient informed consent form and any other written information or document to be provided to the patients.

In case of modifications to the trial protocol, patient informed consent form or any other written information provided to the patients, or to any trial 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 patients' 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 Trial Master File at Guerbet and at the investigational sites in their respective Investigational Site File (ISF).

Notification 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 9 of the present protocol.

Notifications of non-compliance / deviations to IRB/IEC and Regulatory/Competent Authority will be made according to national requirements of participating countries and according to individual IRB/IEC requirements when applicable.

13.3 Patient Informed Consent

Prior to participation, all patients must confirm their free and voluntary willingness to participate in the trial. This confirmation is obtained in writing after having received a full oral and written explanation on the trial:

- Aims, methodology and duration of the trial;
- Potential benefits, foreseeable risks and inconveniencies related to the trial;
- Rights and responsibilities of patients, with particular emphasis on the right to refuse trial 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 trial at the investigational site.

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

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

When the consent may not be directly obtained in writing, a legal representative/impartial witness may be involved in the process and confirm in writing that the patient consented freely and voluntarily. Such involvement(s) must be fully documented in the patient's medical records and the informed consent.

The information of patients may only be conducted by qualified investigational site personnel, whose involvement and responsibility for patient 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 patient informed consent or of any other document to be provided to the patients, the IRB/IEC approval must be obtained prior to implementing the new document(s). Patients who already consented may be asked to confirm their willingness to continue participating in writing. In any case, the same information and consent process as described above must be followed.

13.4 Trial Records and Archiving

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial -related duties and functions conducted at the trial site.

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

At the end of the trial, 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 trial completion. Sites should obtained Guerbet written approval before destroying trial documents.

14 QUALITY CONTROL / QUALITY ASSURANCE

14.1 Direct Access to Source Data/Documents

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

The investigator must guarantee the safety of the trial 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 patient data before collection by Guerbet. Especially the name and address of the patients will be deleted from any medium such as clinical eCRF, document for biological results, X-Ray films or digital supports.

- For this trial, the following will be considered as source data: patients' medical files, images.
- If computerized medical files are used, the system must be evaluated by Guerbet (or representative): In case printing of files is not possible, the computerized system must be validated and access should be granted to Guerbet or its representative.

If the computerized system is not validated, the investigator must, at the start of the trial, print, sign and date all the medical files of all patients and during the trial, print, sign and date in real time each data entry and each data change.

14.2 Clinical Monitoring

Before the trial is conducted at a given investigational site and until the trial is completed/terminated at the same given investigational site, Guerbet will mandate a representative to perform a close monitoring of the trial conduct that will ensure that the investigational site is properly equipped; the staff is adequately experienced and knowledgeable of regulatory and ethical requirements. Monitors contact details will be listed on the trial team list.

The representative will perform regular investigational site visits and report all discussions, patient and IMP data verification performed with particular attention to patients' safety and well-being and trial data accuracy and completeness. All monitoring procedures and requirements will be described in a monitoring plan.

14.3 Clinical Data Handling

14.3.1 *Data Reported in the eCRF*

The clinical eCRF will allow recording of data required by the protocol, except detailed central laboratory results and blinded imaging assessment performed by IBR entered in imaging eCRF.

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

The investigator must attest:

- The authenticity of the data collected in the clinical eCRF;
- The consistence between the data in the clinical eCRF and those in the source documents.

No data entered in clinical eCRF may be considered as source data.

14.3.2 *Data Reported in the clinical eCRF according to patient Status*

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patient to respond to potential queries from regulatory authorities.

Minimal information includes demography, screen failure details (listed on 'end of trial clinical eCRF page), eligibility criteria, and any serious adverse event (SAE). Additional information such as medical history, concomitant medication etc…might be requested in case of SAE.

For patients discontinued from the trial after randomization, all data available at the time of discontinuation will be reported in the medical file and the clinical eCRF (e.g.: inclusion data, safety data, administration data, imaging data, reason for premature discontinuation…). 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 patient withdraws consent for further data collection/participation for/in the trial.

14.3.3 *Data Management System*

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

Data processing and control will be closely managed by Guerbet's representative.

14.4 Audits and Inspections

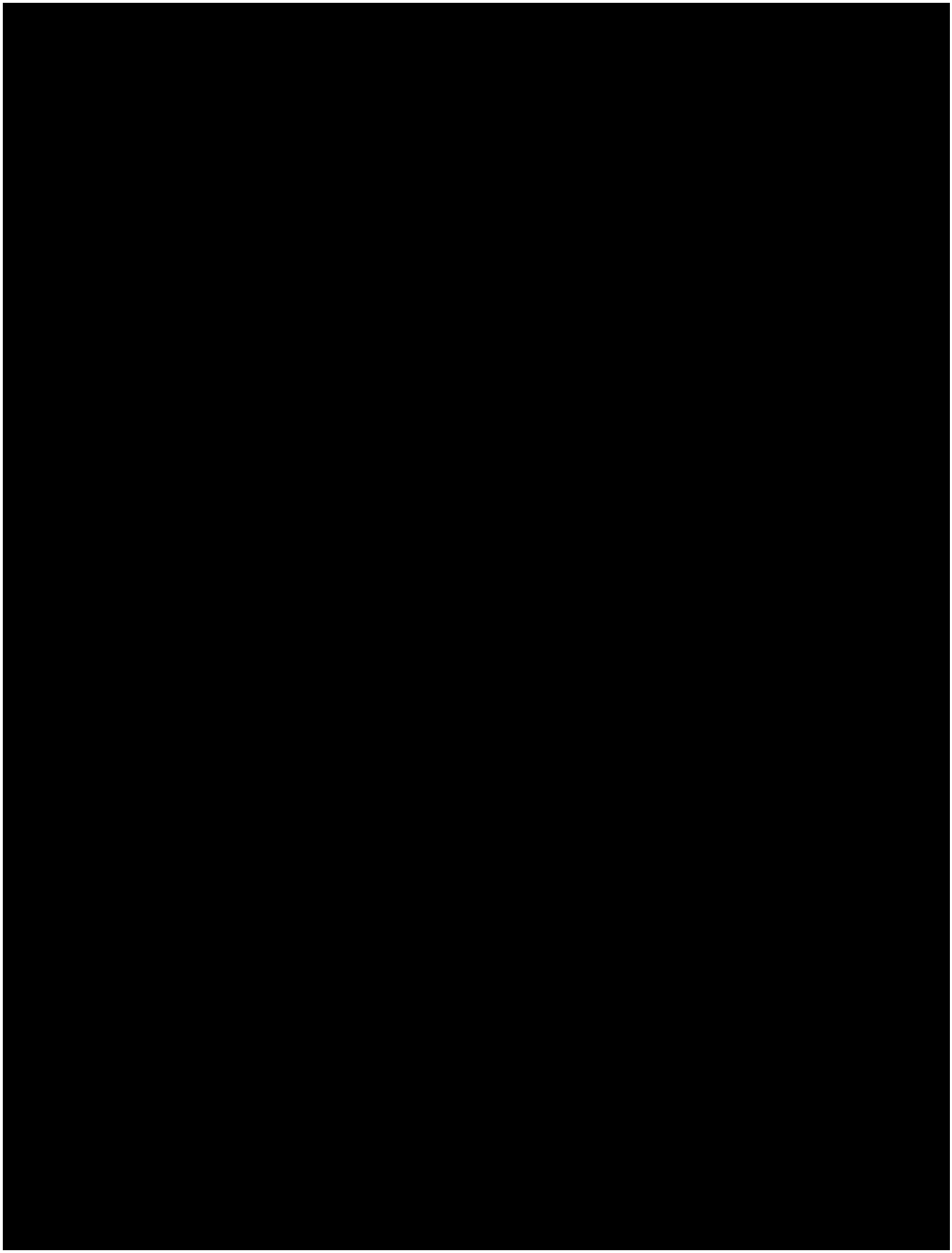
At any time during the trial conduct, Guerbet may mandate a representative to perform an audit of investigational sites in order to assess compliance with the regulatory and ethical requirements, the trial protocol and related instructions and to assess the accuracy and completeness of data generated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

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

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

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

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



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17 COMPANY LIABILITY INSURANCE

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

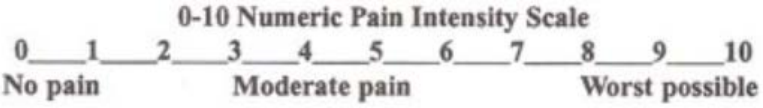
Furthermore, Guerbet and the investigator undertake to comply with the locally applicable legal requirements with respect to insurance.

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 trial protocol,
- An accident occurring for a patient whose consent to participation was not adequately collected.

18 APPENDICES

18.1 Numeric Pain Intensity Scale



Circle the number corresponding to the pain intensity.

18.2 Volume of IMP injection by body weight

		gadopiclenol (0.5M)	gadobutrol (1M)
Adults		***Dose (mmol/kg)***	***Dose (mmol/kg)***
		0.05	***0.1***
		Dose (ml/kg)	**Dose (ml/kg)**
		0.1	**0.1**
Body Weight		**Volume (mL)**	**Volume (mL)**
Kilograms (kg)	**Pounds (lb)**		
40	88	4	4
50	110	5	5
60	132	6	6
70	154	7	7
80	176	8	8
90	198	9	9
100	220	10	10
110	242	11	11
120	264	12	12
130	268	13	13
140	308	14	14
150	330	15	15