Performance of Elucirem® (gadopiclenol) in Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) perfusion of brain gliomas

Phase IIIb Clinical Trial

EudraCT No.: 2022-002720-12

COORDINATING INVESTIGATOR or International coordinator (if not a participating site)

NOT APPLICABLE

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PROTOCOL SYNOPSIS

Trial Title: Performance of Elucirem® (gadopiclenol) in Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) perfusion of brain gliomas Phase IIIb Clinical Trial	
Trial Product(s): Elucirem® (G03277)	Active Ingredient(s): gadopiclenol
EudraCT No.: 2022-002720-12	
Potential Participating countries (Potential Number of sites): Trial involving approximately 10 sites in 3-4 countries	

Trial Objectives

Primary objective:

To demonstrate the non-inferiority of DSC-MRI perfusion using Elucirem® (gadopiclenol) at 0.05 mmol/kg compared to DSC-MRI perfusion using Dotarem® (gadoterate meglumine) at 0.1 mmol/kg in terms of diagnostic quality of Cerebral Blood Volume (CBV) perfusion map (off-site assessment)

Secondary objectives:

- To evaluate the diagnostic quality of CBV perfusion map for Elucirem® and Dotarem® (on-site assessment)
- To compare the performance of DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg to DSC-MRI using Dotarem® at 0.1 mmol/kg in differentiating glioma grade through the quantification of the relative CBV (rCBV) (off-site assessment)
- To assess the reliability of the T2* signal intensity time curve in terms of confidence in diagnosis in DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg (on-site and off-site assessments)
- To expand the previously established safety profile of Elucirem® at 0.05 mmol/kg in terms of incidence of adverse events

Trial design and methodology

The trial is designed as a prospective, multi-center, randomized, controlled and parallel group comparison.

The Investigational Medicinal Products (IMP) used for the trial are Elucirem® and Dotarem®.

Once informed consent form (ICF) signed, the patients will perform a screening visit (V1) to confirm trial eligibility. The eligible patients will be randomized by Interactive Web Response System (IWRS) to determine the IMP to be injected. They will undergo a DSC-MRI perfusion using Elucirem® or Dotarem® (MRI visit - V2). A safety visit (V3) will be performed 1 day after the MRI visit by phone. Confirmation of tumor grade diagnosis, if available, will be collected up to 30 days after visit 2.

The randomization scheme will allocate patients in a 1:1 ratio to the two parallel arms. Stratification by glioma grades (low grades versus high grades) between the two arms will be managed by IWRS based on the diagnosis collected at screening.

Images will be evaluated by both on-site and off-site readers.

For on-site reads, at least one experienced neuroradiologist will be appointed in each investigational site at the start of the trial to read perfusion images of patients included at the site.

For off-site reads, all images will be sent to an imaging laboratory which will prepare the images for evaluation. The off-site images evaluation will be performed by two independent blinded radiologists (IBR) experienced in perfusion MRI and brain tumors. In case of discordance, a consensus meeting will be organised in order to reach an agreement.

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.

For this study, only off-site readers will be blinded to the nature of the IMP injected.

During the trial, the safety of the patients will be monitored and assessed based on the reporting of adverse events (AE).

Number of patients

138 patients to be enrolled, in order to have 124 evaluable patients

Eligibility criteria

Inclusion criteria:

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

1. Female or male adult patient (patient having reached legal majority age).
2. Patient with naive or recurrent primary glial tumor detected at a previous Computed Tomography (CT) or MR imaging, and scheduled for a follow-up contrast-enhanced MRI. Tumor grade (confirmed or highly suspected) should be available in patients' medical records.
3. Patient or, if the patient is unable to provide informed consent, the patient's legally acceptable representative and/or impartial witness, having read the information and having provided patient's consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.
4. Patient affiliated to national health insurance according to local regulatory requirements.

Non-inclusion criteria:

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

1. Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other Gadolinium-Based Contrast Agents (GBCA) (such as hypersensitivity, post-contrast acute kidney injury).
2. Patient presenting with any contraindication to MRI examinations.

3. Post treatment patient presenting with pseudo-progression instead of tumor recurrency.
4. Patient presenting with severe renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² assessed within 1 week prior to contrast agent injection.
5. Patient having received any contrast agent (for MRI or CT) within 3 days prior to IMP administration or scheduled to receive any contrast agent within 24 hours after IMP administration.
6. Pregnant female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative pregnancy test within 1 day prior to trial MRI and must be using medically approved contraception method until the last trial visit).
7. 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.
8. Patient previously randomized in this trial.
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.

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

Investigational Medicinal Products administration

Investigational Medicinal Product (IMP) 1:

Name: Elucirem® (gadopiclenol) (formulation G03277)

Pharmaceutical form: 20-mL vial containing 15 mL of solution presented as a sterile, clear, ready-to-use aqueous solution for injection.

Concentration: 0.5 M

Route and method of administration:

Elucirem® will be intravenously (IV) administered at 0.05 mmol/kg using a power injector at the injection rate of minimum 4 mL/second, followed by a 20-mL 0.9% saline flush at the same injection rate.

Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of Elucirem® should not exceed 0.05 mmol/kg.

Investigational Medicinal Product (IMP) 2:

Name: Dotarem® (gadoterate meglumine)

Pharmaceutical form: 20-ml vial containing 20 mL of solution presented as a sterile, clear, ready-to-use aqueous solution for injection.

Concentration: 0.5 M

Route and method of administration:

Dotarem® will be intravenously (IV) administered at 0.1 mmol/kg using a power injector at the injection rate of minimum 4 mL/second, followed by a 20-mL 0.9% saline flush at the same injection rate.

Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of Dotarem® should not exceed 0.1 mmol/kg.

Trial duration for patients:

Minimum trial duration for patients: 2 days, if V1 and V2 are done on the same day.

Maximum trial duration for patients: 9 days, if the screening period lasts 7 days.

Maximum trial duration for collection of data: 37 days, if the screening period lasts 7 days and a biopsy or surgery is done 30 days after the MRI.

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

Imaging Protocol

The imaging procedures will be performed using a 1.5T or a 3T MRI scanner, equipped with echo-planar imaging (EPI) capabilities, that can perform the required sequences.

Brain imaging protocol will include:

Unenhanced sequences:

- Axial 3D T1WI GRE
- Axial 2D T2WI T(F)SE
- Axial 2D FLAIR

Contrast-enhanced sequences:

- Perfusion imaging: Axial DSC T2* EPI
- Axial 3D T1WI GRE

Perfusion DSC sequences will be post processed with a dedicated software, which will generate CBV map.

Imaging protocol will be fully described in an imaging manual that will be provided to investigational sites.

Evaluation criteria

CBV map will be generated through post-processing software for each DSC-MRI perfusion.

Technical adequacy of CBV map will be determined by on-site and off-site readers using a 4-point scale with the following grades: non-diagnostic, poor, fair, good. Images are to be considered technically adequate if evaluation is possible despite any artifacts that might partially compromise image quality. Images are considered technically non-diagnostic if artifacts completely compromise image interpretability.

The major artifact according to the list below will be recorded:

1 = Movement artifacts
2 = T2* artifacts
3 = EPI distortion
4 = Other, to be specified

Only for images considered technically adequate, the following evaluations will be performed:

Primary evaluation criterion:

Diagnostic quality of the CBV map will be assessed by off-site readers using a 4-point scale with the grades: poor, fair, good or excellent as defined below:

1: Poor: IC; EC; BG not distinguishable & CGM; SCWM; DWM not distinguishable

2: Fair: IC; EC; BG partially distinguishable on AS & CGM; SCWM; DWM partially distinguishable on 2S

3: Good: IC; EC; BG well distinguishable on 2S & CGM; SCWM; DWM well distinguishable on 2S

4: Excellent: IC; EC; BG well distinguishable on AS & CGM; SCWM; DWM well distinguishable on 2S

IC=Internal Capsule; EC=External Capsule; BG=Basal Ganglia; CGM=Cortical normal appearing Gray Matter; SCWM=Sub-Cortical normal appearing White Matter; DWM=Deep normal appearing White Matter; AS=all slices; 2S=not more than 2 slices.

Secondary evaluation criteria:

- ***The following assessments will be performed with Elucirem® and Dotarem®:***
    - **Diagnostic quality of the CBV map** will be assessed by on-site readers using the same 4-point scale as the one used for primary evaluation criterion
    - **Assessment of rCBV and T2* signal intensity time curve**
        - **Quantification of the relative CBV** for differentiating tumor grade (off-site assessment)

          The rCBV will be calculated on the CBV perfusion maps generated for each DSC-MRI perfusion. The regions of interest (ROIs) will be placed by off-site readers on the tumor for providing tumor CBV and also on normal tissue (contralateral normal-appearing white matter) for providing referenced CBV.

          To be sure that the imaged tumor is the same as the tumor biopsied, results will be matched with the standard of truth for diagnosis of glioma grade. This standard of truth will be histopathological results collected on site (diagnosis based on 2021 WHO classification of Central Nervous System (CNS) tumors).

        - **Evaluation of the T2* signal intensity time curve and assessment** (on-site and off-site assessments)

          T2* signal intensity time curve will be visually assessed by on-site and off-site readers for the reliability of the curve in providing sufficient information for diagnosis purpose. The Full-Width at Half-Maximum (FWHM) and the maximum signal drop will be measured by off-site readers only.

Readers will record their confidence in diagnosis based on the reliability of the curve using a 5-point scale:

1 = nil: very uncertain
2 = poor: uncertain
3 = moderate: moderately certain
4 = high: good certainty
5 = excellent: very certain

- ***The following safety parameters will be assessed:***
    - **Adverse events**, serious or not, related to IMP or not, that occur from the beginning of patient's participation in the trial (Informed Consent Form signature) until the end of the participation.

Statistical methods

Sample size:

The primary objective of the trial is to demonstrate the non-inferiority of DSC MRI perfusion using Elucirem® at 0.05 mmol/kg compared to Dotarem® at 0.1 mmol/kg in terms of diagnostic quality of the CBV perfusion map based on off-site evaluations.

A 12% non-inferiority margin was considered clinically as an unimportant difference and therefore relevant to establish acceptable diagnostic quality of Elucirem® relative to Dotarem®.

Statistical hypotheses

- H0: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} \leq -0.12$

- H1: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} > -0.12$

Sample sizes of 62 in each arm achieve 80% power to detect a difference of 0 when the non-inferiority difference is -0.12. The reference group proportion is 94%. The treatment group proportion is assumed to be 82% under the null hypothesis. The power was computed for the case when the actual treatment group proportion is 94%. The test statistic used is the one-sided Z test (unpooled). The significance level of the test is 2.5% (unilateral, 5% bilateral).

Assuming a 10% drop-out rate, the sample size increases to 138 patients to test that the proportion of patients presenting with images of excellent and good quality in the Elucirem® arm is not inferior to the proportion of patients presenting with images of excellent and good quality in the Dotarem® arm.

Main analyses:

For the diagnostic quality of the CBV perfusion map: non-inferiority will be evaluated by testing whether the lower bound of the two-sided 95.2% Confidence Interval (CI) for difference of "Elucirem®– Dotarem®", in proportion of patients presenting with images of excellent and good quality according to off-site readers, excludes a 12% difference.

In particular, at the final analysis, for both arms the associated two-sided 95.2% CI for the difference will be estimated.

Non-inferiority of Elucirem® over Dotarem® will be demonstrated, at the final analysis, if the lower bound of the two-sided 95.2% CI around the estimated differences in the primary endpoint, proportion of patients presenting with images of excellent and good quality, lies above -12%.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority.

The same analysis (and only at the final one) will be performed for on-site evaluations.

An interim analysis will be performed when 50% of the patients will be assessed in terms of diagnostic quality of the CBV perfusion map.

Non-inferiority of Elucirem® over Dotarem® will be evaluated by testing whether the lower bound of the two-sided 99.8% CI for difference of "Elucirem®– Dotarem®", in proportion of patients presenting with images of excellent and good quality according to off-site readers, excludes a 12% difference.

Again, if non-inferiority of Elucirem® is concluded at the interim analysis, the superiority of Elucirem® compared to Dotarem® will be tested in the same way as described above.

For rCBV evaluated off-site, the Mann-Whitney U-test will be used to compare the two trial arms by tumor grade categorization (high grade on one hand and low grade on the other hand).

The Mann-Whitney U-test will also be used to test the difference in rCBV between patients with high-grade and low-grade gliomas, within each of the two study arms.

These analyses will be performed according to the tumor grade categorization as per stratification (high grades versus low grades) and according to tumor grade categorization as per histological results.

Categorization as per histological results will be the following:

- Grade 1 and Grade 2 = Low grade,
- Grade 3 and Grade 4 = High grade.

For the assessment and evaluation of the T2* signal intensity time curve, off-site FWHM and the maximum signal drop will be compared between the trial arms using a Mann-Whitney U-test.

Moreover, confidence in diagnosis based on the reliability of the curve will be presented for the two trial arms, for on-site and off-site read.

Regarding **safety**, occurrence rates of AEs will be tabulated by trial arms and according to the causal relationship to the IMPs and the procedure itself.

TRIAL FLOW CHART

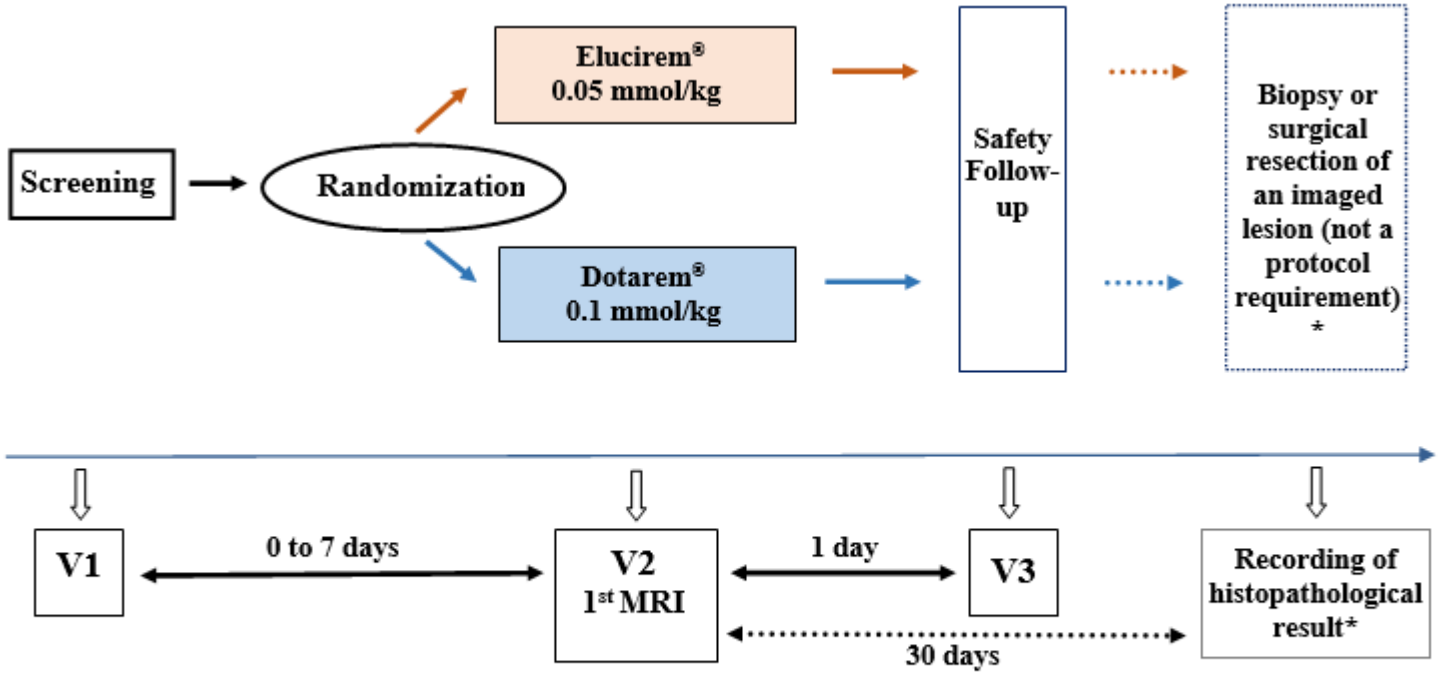
Table 1: Trial flow chart

Time points Evaluation/procedures	**Screening (V1) [1]**	**MRI/Randomization (V2)** *Contrast injection*		**Safety follow-up (V3) [5]**	**Record of histopathology results (Biopsy or surgery)**
	≤7 days	**Prior to MRI**	**MRI**	**1 day after V2**	**Within 30 days of V2**
Informed consent signature	X				
Eligibility criteria	X	X			
Demographic data	X				
Medical history	X				
Patient Imaging history	X				
Body weight		X			
Concomitant treatments	X				
Pregnancy test [2]	X	X			
Local creatinine and eGFR evaluation [3]	X				
IMP injection			X		
Imaging acquisition			X		
Tumor grade diagnosis collection	X				X
IWRS connection	X	X			
Adverse events collection [4]	X				
Procedures/Therapeutic measures	X				

(1) V1 can be performed on the same day as V2.
(2) Urine pregnancy test (if applicable) is to be done on site. Results must be available and negative 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.
(3) eGFR is to be evaluated locally within 1 week before IMP administration. Results must be available prior to administration of IMP and must fulfill the corresponding inclusion criterion.
(4) AEs occurring during the time of the patient's participation in the trial, must be reported and followed as described in Table 3.
(5) Visit 3 will be performed by phone

TRIAL DIAGRAM

Figure 1: Trial diagram



V: visit

Applicable to patients who undergo a biopsy or a surgery within 30 days after the MRI examination

SIGNATURE PAGE

GUERBET MEDICAL EXPERT PPD	Signature: PPD Date: PPD
GUERBET CLINICAL PROJECT MANAGER PPD	Signature PPD Date: PPD
GUERBET BIOSTATISTICIAN PPD	Signature: PPD PPD Date: PPD

COORDINATING INVESTIGATOR **Or International coordinator (if not a participating site)** NOT APPLICABLE	Signature: NOT APPLICABLE Date: NOT APPLICABLE

INVESTIGATOR STATEMENT

I agree to conduct the clinical trial in accordance with the present protocol (and its amendments, if applicable) and to comply with the requirements of the Declaration of Helsinki, the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH) and all other laws and regulations in force on the use of investigational medicinal products.

Name, Title Institution Name Address Telephone e-mail	Signature: Date:

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
ARPS	All Randomized Patients Set
AS	All slices
ATC	Anatomical Therapeutic Chemical
BG	Basal Ganglia
BW	Body Weight
CBV	Cerebral Blood Volume
CGM	Cortical normal appearing Gray Matter
CI	Confidence Interval
CNS	Central Nervous System
CRA	Clinical Research Associate
CT	Computed Tomography
EC	External Capsule
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
DICOM	Digital Imaging and Communication in Medicine
DSC	Dynamic Susceptibility Contrast
DWM	Deep normal appearing White Matter
EPI	Echo Planar Imaging
FAS	Full Analysis Set
FLAIR	Fluid Attenuated Inversion Recovery
FWHM	Full-Width at Half Maximum
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
eGFR	estimated Glomerular Filtration Rate
GRE	Gradient Recalled Echo
IBR	Independent Blinded Reader
IC	Internal Capsule
ICH	International Conference on Harmonization

ICF	Informed Consent Form
ICL	Imaging Core Lab
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INV	Investigator
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intra Uterine Device
IUS	Intra Uterine System
IWRS	Interactive Web Response System
IV	Intravenously
LAM	Lactational Amenorrhoea Method
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mL	Milliliter
NSF	Nephrogenic Systemic Fibrosis
PPS	Per Protocol Set
PT	Preferred Term
rCBV	Relative CBV
ROI	Region Of Interest
2S	Not more than 2 slices
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SCWM	Sub-Cortical normal appearing White Matter
SOC	System Organ Class
SS	Safety Set
SPS	Screened Patient Set
TEAE	Treatment Emergent Adverse Event
T(F)SE	Transient (Fast) Spin Echo
V	Visit
WHO	World Health Organization

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1 INTRODUCTION

1.1 Trial Rationale

Gliomas are the most common primary intracranial tumors, representing 81% of malignant brain tumors [1]. They are considered the most rapidly growing malignancies of the central nervous system, with glioblastoma comprising more than 50% of all gliomas. Early and accurate tumor diagnosis and classification is essential for patient care management, as treatment modalities will significantly differ according to the glioma grade.

Perfusion MRI provides additional information to conventional MRI [2]. This MRI technique can be used to image neovascularization, a hallmark of tumor progression. In this way, perfusion MRI helps to characterize brain gliomas [3]. Perfusion MRI sequence is implemented in the standard imaging protocol of a large number of sites in USA and in Europe [4; 5]. Among MRI perfusion techniques, Dynamic Susceptibility Contrast MRI is the most used perfusion method.

DSC-MRI is a technique in which the first pass of a bolus of GBCA through brain tissue is monitored by a series of T2- or T2*-weighted MR images [6]. The susceptibility effect of the paramagnetic contrast agent leads to a signal loss in the signal intensity-time curve. Using a signal model for susceptibility contrast, the signal information can be converted into a contrast medium concentration -time curve on a voxel-by-voxel basis. Various hemodynamic parameters can be calculated from the concentration-time curve. Among them, relative CBV (rCBV) is the most used parameters. The ratio of rCBV in lesions and in contralateral normal-appearing white matter is often calculated for quantification. It is commonly accepted that CBV reflects tumor neoangiogenesis and correlates with glioma grade [7]. Glioblastoma presents with elevated rCBV due to increased cellular proliferation.

Most DSC perfusion studies are performed using GBCA at 0.1 mmol/kg. Yet there are several reasons for considering reduction of GBCA dose for brain DSC perfusion. The main reasons are safety concerns such as the development of Nephrogenic Systemic Fibrosis (NSF) in at-risk subjects with impaired renal function [8; 9] and the potential retention of gadolinium in tissues even in subjects with normal renal function [10-15].
In the context of the necessity to perform multiple contrast-enhanced MR imaging applications, the use of half dose of gadolinium is to be considered.

Some studies with other GBCA have shown that reduced-contrast-dose (0.05 mmol/kg) DSC perfusion of the brain is comparable with those of the full-dose protocol in terms of diagnostic quality of perfusion CBV maps [16; 17]. In addition, no significant difference in CBV mean value was found.

Elucirem® (gadopiclenol) is a new chemical entity discovered and developed by Guerbet. It is a non-ionic macrocyclic gadolinium complex, of high kinetic stability, intended to be used in human, by intravenous administration, as a contrast agent for MRI with variable indications. Its safety and efficacy when used at the dose of 0.05 mmol/kg body weight (BW) in adults and in children of 2 years and older have been proven through the global clinical development program of gadopiclenol.

The present clinical trial aims to study the performance of Elucirem® at 0.05 mmol/kg in DSC-MRI perfusion of brain gliomas and to demonstrate that it is as efficient as Dotarem® at 0.1 mmol/kg for qualitative and quantitative CBV perfusion evaluation.

1.2 Background

During the global clinical development program of Elucirem® nine studies were conducted since 2013. In total more than 1 065 patients/healthy volunteers were exposed to Elucirem® at different doses (up to 0.3 mmol/kg). A Phase IIb trial has been conducted in 280 adults with CNS diseases. This was a dose-response trial with a cross-over design allowing the comparison of contrast quality provided by each of the 4 tested gadopiclenol doses (0.025, 0.05, 0.1 and 0.2 mmol/kg) towards gadobenate dimeglumine at the dose of 0.1 mmol/kg. Elucirem® at 0.05 mmol/kg was identified as the lowest dose showing efficacy similar to the reference product [18]. In a randomized phase III trial including 256 randomized CNS patients, the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of lesion visualization was demonstrated and a good safety profile was observed.

1.3 Benefit/Risk Assessment

Patient may not receive direct benefit for participating in this research.

The following potential safety concerns were identified for surveillance based on currently available nonclinical and clinical study data and therapeutic class effects for both trial products:

- Injection site tolerance
- Nephrogenic Systemic Fibrosis
- Hypersensitivity
- Seizures
- Nephrotoxicity
- Gadolinium deposition in brain and other organs/tissues

Minimization measures have been implemented in this protocol for any of those concerns (section 5.1.3).

2 TRIAL OBJECTIVES

2.1 Primary Objective

To demonstrate the non-inferiority of DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg compared to DSC-MRI perfusion using Dotarem® at 0.1 mmol/kg in terms of diagnostic quality of CBV perfusion map (off-site assessment).

2.2 Secondary Objectives

- To evaluate the diagnostic quality of CBV perfusion map for Elucirem® and Dotarem® (on-site assessment)
- To compare the performance of DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg to DSC-MRI using Dotarem® at 0.1 mmol/kg in differentiating glioma grade through the quantification of the relative CBV (off-site assessment)
- To assess the reliability of the T2* signal intensity time curve in terms of confidence in diagnosis in DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg (on-site and off-site assessments)

- To expand the previously established safety profile of Elucirem® at 0.05 mmol/kg in terms of incidence of adverse events

3 TRIAL DESCRIPTION

3.1 Protocol Design

The trial is designed as a prospective, multi-center, randomized, controlled and parallel group comparison.

Once informed consent form (ICF) signed, the patients will perform a screening visit (V1) to confirm trial eligibility. The eligible patients will be randomized by Interactive Web Response System (IWRS) to determine the IMP to be injected. They will undergo a DSC-MRI perfusion using Elucirem® or Dotarem® (MRI visit - V2). A safety visit (V3) will be performed 1 day after the MRI visit by phone. Confirmation of tumor grade diagnosis, if available, will be collected up to 30 days after visit 2.

The randomization scheme will allocate patients in a 1:1 ratio to the two parallel arms. Stratification by glioma grades (low grades versus high grades) between the two arms will be managed by IWRS based on the diagnosis collected at screening.

Images will be evaluated by both on-site and off-site readers.

For on-site reads, at least one experienced neuroradiologist will be appointed in each investigational site at the start of the trial to read perfusion images of patients included at the site.

For off-site reads, all images will be sent to an Imaging Core Laboratory (ICL) which will prepare the images for evaluation. The off-site images evaluation will be performed by two IBR experienced in perfusion MRI and brain tumors. In case of discordance, a consensus meeting will be organised in order to reach an agreement.

An imaging 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.

For this study, only off-site readers will be blinded to the nature of the IMP injected.

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

During the trial, the safety of the patients will be monitored and assessed based on the reporting of adverse events (AE).

This trial will be an international trial conducted in several European countries.

3.2 Justification for dose

The safe and lowest effective clinical dose of gadopiclenol identified in phase IIb trial and confirmed by the results of the two phase III trials is 0.05 mmol/kg body weight. This dose will be used for gadopiclenol for this trial.

Dotarem® 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 patients' participation*

Minimum trial duration for patients: 2 days, if V1 and V2 are done on the same day.

Maximum trial duration for patients: 9 days, if the screening period lasts 7 days.

Maximum trial duration for collection of data: 37 days, if the screening period lasts 7 days and a biopsy or surgery is done 30 days after the MRI.

The trial includes a maximum of 3 visits and the record of histopathology results:

- Screening visit (V1): up to 7 days prior to inclusion (V1 could be done on the same day as the imaging visit (V2) if all the inclusion/non-inclusion criteria are met).
- MRI/Randomization visit (V2): the visit will consist of Elucirem® or Dotarem® injection and MRI procedure
- Safety visit (V3): 1 day after MRI examination

Record of histopathology results from a biopsy or a surgery will be done up to 30 days after the MRI examination.

3.3.2 *End of trial*

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

3.4 Interim Analysis

An interim analysis will be performed when 50% of the patients will be assessed in terms of diagnostic quality of images by the off-site readers.

3.5 Trial Committee(s)

An internal committee will assess efficacy results when the results of the interim analysis will be available. See section 12 for details.

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 with naive or recurrent primary glial tumor detected at a previous CT or MR imaging, and scheduled for a follow-up contrast-enhanced MRI. Tumor grade (confirmed or highly suspected) should be available in patients' medical records.
3. Patient or, if the patient is unable to provide informed consent, the patient's legally acceptable representative, having read the information and having provided patient's consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.
4. Patient affiliated to national health insurance according to local regulatory requirements.

4.2 Non-Inclusion Criteria

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

1. 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).
2. Patient presenting with any contraindication to MRI examinations.
3. Post treatment patient presenting with pseudo-progression instead of tumor recurrency.
4. Patient presenting with severe renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² assessed within 1 week prior to contrast agent injection.
5. Patient having received any contrast agent (MRI or CT) within 3 days prior to IMP administration or scheduled to receive any contrast agent within 24 hours after IMP administration.
6. Pregnant female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative pregnancy test within 1 day prior to trial MRI and must be using medically approved contraception method* until the last trial visit).
7. 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.
8. Patient previously randomized in this trial.
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.

**Highly effective birth controlled method includes: abstinence (defined as refraining from heterosexual intercourse during the entire trial participation), 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, vasectomized partner (vasectomized partner is a highly effective*

birth control method provided that partner is the sole sexual partner of the female patient and that the vasectomized 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.

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: Elucirem® (formulation G03277)

Pharmaceutical form: 20-mL vial containing 15 mL of solution presented as a sterile, clear, ready-to-use aqueous solution for injection.

Concentration: 0.5 M

Route and method of administration:

Elucirem® will be intravenously (IV) administered at 0.05 mmol/kg using a power injector at the injection rate of minimum 4 mL/second followed by a 20-mL 0.9% saline flush at the same injection rate.

Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of Elucirem® should not exceed 0.05 mmol/kg. The volume of the preload bolus, if any, should be collected in eCRF. Sufficient IMP must be allocated to one patient by IWRS.

Please refer to the Investigator Brochure for more information on Elucirem®.

5.1.2 *Investigational Medicinal Product 2*

Name: Dotarem® (gadoterate meglumine)

Pharmaceutical form: 20-mL vial containing 20 mL of solution presented as a sterile, clear, ready-to-use aqueous solution for injection.

Concentration: 0.5 M

Route and method of administration:

Dotarem® will be intravenously (IV) administered at 0.1 mmol/kg using a power injector at an injection rate of minimum 4 mL/second followed by a 20-mL 0.9% saline flush at the same injection rate.

Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of Dotarem® should not exceed 0.1 mmol/kg.

Sufficient IMP must be allocated to one patient by IWRS.

Please refer to the SmPC for more information on Dotarem®.

5.1.3 *Precautions for use for both Investigational Medicinal Products*

Injection site tolerance

Caution during administration is necessary to avoid any extravasation. In case of extravasation, the injection must be stopped immediately. In case of local reactions, evaluation and treatment should be carried out as necessary.

Hypersensitivity

As with other GBCAs, hypersensitivity reactions may occur with Elucirem® and could be life-threatening. Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can be either immediate (less than 60 minutes) or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable.
During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast medium must be discontinued immediately and – if necessary - specific therapy instituted. A venous access should thus be kept during the entire examination. In order to permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

The risk of hypersensitivity reactions may be higher in patients with history of:
- Previous reaction to a GBCA.
- Bronchial asthma
- Allergy

As with other GBCAs, there is a possibility that the injection of Elucirem® or Dotarem® may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use Elucirem® must be made after careful evaluation of the benefit/risk ratio.

Seizures

As with other GBCAs, special caution is necessary in patients with a lowered threshold for seizures. All equipment and drugs necessary to counter any convulsion which may occur must be made ready for use beforehand.

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 Elucirem® and Dotarem® will be performed by Guerbet (or its designee).

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

IMP will consist in a box that contains one 20-mL vial containing 15 mL of Elucirem® or 20 mL of Dotarem®.

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 30°C or below. It should not be 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 of the two arms. One arm consists of the use of Elucirem® as contrast agent, the other arm consists in the use of Dotarem® as contrast agent (see Figure 1).

The randomization scheme will allocate patients in a 1:1 ratio to the two parallel arms. Stratification by glioma grades (low grades versus high grades) between the two arms will be managed by IWRS based on the diagnosis collected at screening.

At visit 2, once all the inclusion /non-inclusion criteria 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 contrast medium allocated for the enhanced MRI procedure.

In case of problem of IMP allocation (e.g. wrong IMP administered to a 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*

Off-site image readings of all patients will be evaluated in blinded conditions regarding the contrast agent injected as described in Section 8.4. This is to ensure that there is no bias in the evaluation of the primary criterion.

Except off-site readers, all parties will be open.

5.3.3 *Individual Trial Treatment Unblinding*

Not applicable

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

The investigator, the 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's source document and eCRF.

The volume (mL) of IMP to be injected to the patients will be rounded 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)

6 CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

Any medication, including homeopathic products, premedication, 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 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 administration, after 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 GBCA. 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.

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists: these medicinal products decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders: the radiologist must be informed before injection of gadolinium complexes, and resuscitation equipment must be at hand.

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.

6.1.2 *Prohibited Concomitant Medications*

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

6.2 Concomitant Procedures

Not applicable

7 EVALUATION CRITERIA

CBV map will be generated through post-processing software for each DSC-MRI perfusion.

Technical adequacy of images will be determined by on-site and off-site readers using a 4-point scale with the following grades: non-diagnostic, poor, fair, good. Images are to be considered technically adequate if evaluation is possible despite any artifacts that might partially compromise image quality. Images are considered technically non diagnostic if artifacts completely compromise image interpretability.

The major artifact according to the list below will be recorded:

1 = Movement artifacts
2 = T2* artifacts
3 = EPI distortion
4 = Other, to be specified

Only for images considered technically adequate, the evaluations of primary and secondary criteria will be performed.

7.1 Primary Criterion

Diagnostic quality of CBV map generated will be assessed by off-site readers according to the following 4-point scale:

1: Poor: IC; EC; BG not distinguishable & CGM; SCWM; DWM not distinguishable

2: Fair: IC; EC; BG partially distinguishable on AS & CGM; SCWM; DWM partially distinguishable on 2S

3: Good: IC; EC; BG well distinguishable on 2S & CGM; SCWM; DWM well distinguishable on 2S

4: Excellent: IC; EC; BG well distinguishable on AS & CGM; SCWM; DWM well distinguishable on 2S

IC=Internal Capsule; EC=External Capsule; BG=Basal Ganglia; CGM=Cortical Normal Appearing Gray Matter; SCWM=Sub-Cortical Normal Appearing White Matter; DWM=Deep Normal Appearing White Matter; AS=all slices; 2S=not more than 2 slices.

7.2 Secondary Criteria

7.2.1 *Diagnostic quality of CBV map*

Diagnostic quality of CBV map will be assessed by on-site readers according to the 4-point scale poor/fair/good/excellent as described in section 7.1.

7.2.2 *Assessment of rCBV and T2* signal intensity time curve*

7.2.2.1 Quantification of the relative CBV for differentiating tumor grade (off-site assessment)

For each DSC-MRI perfusion, the rCBV will be calculated on the generated CBV perfusion map. The regions of interest (ROIs) will be placed by off-site readers on the tumor for providing tumor CBV and also on normal tissue (contralateral normal-appearing white matter) for providing referenced CBV.

To be sure that the imaged tumor is the same as the tumor biopsied, localization and size of the tumor assessed by the off-site readers will be matched with the standard of truth for grading gliomas. Standard of truth will be histopathological results collected on site (diagnosis based on 2021 WHO classification of CNS tumors).

7.2.2.2 Evaluation of the T2* signal intensity time curve and assessment (on-site and off-site assessment)

T2* signal intensity time curve will be visually assessed by on-site and off-site readers for the reliability of the curve in providing sufficient information for diagnosis purpose. If the curve is assessed as reliable, the full-width at half-maximum (FWHM) and the maximum signal drop will be measured by off-site readers only.
Readers will record their confidence in diagnosis based on the reliability of the curve using a 5-point scale:

1 = nil: very uncertain
2 = poor: uncertain
3 = moderate: moderately certain
4 = high: good certainty
5 = excellent: very certain

An overview of the imaging evaluation criteria to be assessed by the on-site reader (investigator (INV)) and the Independent Blinded Readers (IBR) is provided in the table below:

Table 2: Allocation of imaging evaluation criteria assessment per type of reader

Evaluation criteria	Readers
Technical adequacy of CBV map	IBR/INV
Diagnostic quality of CBV map	IBR/INV
r-CBV quantification	IBR
Visual assessment of T2* signal intensity time curve	IBR/INV
Maximum signal drop and FWHM T2* signal intensity time curve assessment	IBR

7.2.3 *Recording of Adverse events*

Adverse events (AE), serious or not, related to IMP or not, that occur from the beginning of patient's participation in the trial (Informed Consent Form signature) will be recorded until the end of the participation (see section 9.1.2).

In case of AE, the investigator should closely monitor patient safety for example through clinical laboratory parameters obtained locally as per site standard practice.

No vital signs and no lab parameters measurements (other than eGFR) are requested per the trial protocol, but investigators are encouraged to perform those measurements so that baseline values are available in case of adverse event occurrence.

8 TRIAL SCHEDULE AND PROCEDURES

The schedule of time and events to be performed is given in Table 1.

8.1 Trial Schedule

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

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;
- An Identification Number will be attributed to the patient via IWRS;
- Checking of all eligibility criteria;
- Demographic data (sex, self-reported race/ethnic data, age) will be collected;
- Documentation of relevant medical history/current medical condition present before signing the informed consent including trial disease (naive/recurrent tumor, localization, tumor grade: low grade or high grade);
- Documentation of the last CT or MRI detecting the trial disease;
- Patient imaging history related to GBCA (previous examination(s), number of examinations, adverse reaction);
- Review and recording of concomitant treatments;
- Blood sample collection for local dosage of serum creatinine and checking that eGFR is ≥ 30 mL/min/1.73 m^2. Can be done within 1 week prior to MRI. Results should be obtained prior to randomization.
- A urine pregnancy test should be performed for all women of childbearing potential and must be negative. Results will be recorded on source documentation and reported in eCRF.
- IWRS connection for recording the patient screening visit.
- Trial MRI visit needs to be scheduled within 7 days (or can be performed on the same day if all the inclusion/non-inclusion criteria are met).

If a patient is screen failed, this new patient status should be recorded in the IWRS.

8.1.2 *MRI/Randomization Visit – Visit 2 – Day 1*

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

Procedures to be performed prior to IMP administration:

- Checking of all the eligibility criteria;
- Measurement of body weight;
- Any changes in concomitant treatments/procedures/therapeutic measures since the last visit will be documented;
- A urine pregnancy test should be performed for all women of childbearing potential and must be negative. Results will be recorded on source documentation and reported in eCRF. If V2 is done the same day as V1, only one test will be performed.
- Assessment of AEs will be documented (see section 9);
- IWRS connection will be done to randomize the patient and to obtain the IMPs box number.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required sequences specified in section 8.2.2).
- IMP (Elucirem® or Dotarem®) will be injected intravenously (IV) at the appropriate dose using a power injector with a flow rate of minimum 4 mL/second. This will be followed by a saline flush of a 20 mL bolus of 0.9% saline delivered at the same flow rate. Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of IMP (Elucirem® or Dotarem®) should not exceed 0.05 mmol/kg or 0.1 mmol/kg, respectively.
- The following information will be documented in the source document and recorded in eCRF
- : date and time of contrast agent injection, actual volume administered (documentation of difference from theoretical volume), actual injection rate, overdose (if any), number of vials dispensed, IMP box number(s), injection of saline flush (yes/no, volume), preload bolus (yes/no, volume).

8.1.3 *Safety Visit – Visit 3 – 1 day post visit 2*

The safety visit (V3) will be performed by phone. During this visit, the following assessments or tasks will be performed:

- Use/change of concomitant treatments / procedures / therapeutic measures will be documented;
- Assessment of AEs will be documented.

8.1.4 *Record of histopathology results – Within 30 days of V2*

For patients undergoing biopsy or surgery within 30 days of visit 2, the result of histopathology will be recorded. The date and type of exam (surgery, biopsy) as well as the tumor grade diagnosis are to be recorded.

8.2 Imaging Characteristics

8.2.1 *Equipment*

The imaging procedures will be performed using a MRI scanner, equipped with echo-planar imaging capabilities, that can perform the required sequences.

MRI units with 1.5T or 3T magnetic field will be used regardless of the manufacturer. The following information must be recorded: the manufacturer and field strength of the MRI device.

8.2.2 *Imaging protocol*

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

The required sequences and parameters per patient for Elucirem® and Dotarem® should be as similar as possible. Details on required sequence and parameters will be provided in the Imaging Manual.

Brain imaging protocol will include:

Unenhanced sequences:

- Axial 3D T1WI GRE
- Axial 2D T2WI T(F)SE
- Axial 2D FLAIR

Contrast-enhanced sequences:

- Perfusion imaging: Axial DSC T2* EPI
- Axial 3D T1WI GRE

It is not allowed to add any sequence between contrast agent injection and perfusion imaging.

8.3 On-Site Reading of Images

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

For each investigational site, one neuroradiologist experienced in MRI perfusion and brain tumors will be appointed at the start of the trial to read images of patients included at the site.

8.4 Off-Site Reading of Images

Off-site image 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 an imaging core laboratory (ICL), 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. Scalar information in the MR images will be preserved. A complete audit trail of any changes to the file headers will be maintained.

The blinded image evaluations will be performed by 2 independent blinded readers experienced in brain tumor and perfusion imaging. In case of discordance, a consensus meeting will be organised in order to reach an agreement. The following criterion will be concerned by the consensus in case of discordance:

- The localization of the lesion
- The diagnostic quality of the CBV map (primary criterion).
- rCBV quantification (consensus in the glioma grade, not in the rCBV value)
- Visual evaluation of the T2* signal intensity time curve, including the confidence in the diagnosis.

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 the ICL) will document the imaging tasks and obligations of the investigational site in an Imaging Manual. As defined in section 8.2, 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 ICL (if applicable).

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

8.4.2 *Site Qualification*

Guerbet's agent (Clinical Research Organization (CRO), ICL or monitors) will perform pre-trial site selection. This selection will allow to ensure that the imaging protocol can be performed by the site, are programmed and prepared prior to enrolment of the first patient and that the Imaging Manual will be accurately followed by the site.

8.4.3 *Receipt and Tracking of Images*

Guerbet (or the ICL) will request that sites submit anonymous images to the ICL in a format that will be agreed prior to trial start. Images will be tracked in the database of the ICL.

8.4.4 *Perfusion post processing software*

Perfusion sequences will be post processed by an adequate software, which allows CBV perfusion maps generation. Off-site evaluation will be performed using the same perfusion post processing software for the two IBR.

Regarding the on-site evaluation, each investigating site will use its own perfusion post processing software.

8.4.5 *Image Processing and Quality Check*

Images received by the ICL as digital data will be translated 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 ICL 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 ICL will follow-up on all cases requiring remedial action by the sites. Guerbet (or the ICL) may conduct site training for investigator sites with recurring image quality issues.

8.4.6 *Independent Blinded Readers Training*

Two independent readers with expertise in MRI perfusion of brain gliomas, 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.

The 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 Imaging 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.

8.4.7 *Image Randomization*

When sufficient 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.

8.4.8 *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 locked).

In case of discordance between the two readers, a consensus meeting will be organized in order to reach an agreement. The process will be described in the blinded Imaging Evaluation Charter.

8.4.9 *Inter & Intra-reader Variability Assessment*

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

Inter-reader variability will be evaluated on the whole set of trial patients, since each patient will be read by two 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 after an enough number of 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.

8.4.10 *Lesion tracking/Matching*

Lesion matching will be performed as an independent off-site procedure. The purpose is to guarantee an unambiguous assignment (matching) of the lesions between histopathology and consensus reads for rCBV quantitative evaluations. It will be carried out by a third IBR in blinded condition based on the consensus read results and histopathological data lesion identification (size, location). Once the concordance process is done, a correspondence/tracking lesion table should be obtained, so that lesions could be compared for the analysis.

8.4.11 *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.

9 SAFETY REPORTING

The Investigator will report to Guerbet any adverse event whether related or not to the investigational medicinal products, serious or not, that occurred in a trial patient during its participation to the trial. Special situations such as treatment 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 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).

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

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 medically 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 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 eCRF according to the table below.

Table 3: Collection and reporting of AEs throughout and after the trial

Periods and types of AEs to be reported	**Screening (V1)**	**From MRI/Randomization (V2) to Safety follow-up visit (V3)**	**From follow-up visit (V3) to biopsy or surgery (within 30 days of V2)**	***After biopsy or surgery***
Not related Non-serious AEs	X**	X		
Not related SAEs	X	X	X	
Adverse Event of Special Interest	X	X	X	
Related* AEs (serious or not)	X	X	X	X
Pregnancy cases	NA	X	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.

Any lab results available in medical records could be asked to site for AE assessment.

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 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 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 during the administration (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.
- **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 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 eCRF ("procedures/therapeutic measures" section).
  - Trial discontinuation: the AE leads to a trial discontinuation,
- **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).

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 (F001406) 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 by 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 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 to onset of the event
- End date of the event (will be reported in a follow-up report if the event is still ongoing at the time of 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 (F001406).

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 (F018362) 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), Independent Ethics Committee (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 Independent Ethics Committee/ Institutional Review Board (IEC/IRB), if applicable.

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 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" for MRI examinations.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose, which is above 0,3 mmol/kg for the Elucirem® and Dotarem®.

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 that is discovered after the ICF signature must be reported to Guerbet Pharmacovigilance *via* the report form for SAE, AESI or pregnancy (F001406) (see section 9.2.2) unless the conception date is over 1 week 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.

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

Specific forms "history and start of pregnancy" (F006030) and "course and outcome of pregnancy" (F006033) 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 (F001406).

The AESI for this protocol is the following: Nephrogenic Systemic Fibrosis (NSF). This disease affects the whole body (including kidney) but has its most prominent and visible effects in the skin, and mostly occurs in case of preexisting renal deficiency. NSF has been observed with gadolinium-based contrast agents, more frequently with the linear ones. The NSF has not been observed with Elucirem®, that is not a linear GBCA. In case of any suspicion of NSF, complementary investigation should be performed.

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),
- 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, 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

9.5 Unblinding Procedures

Not applicable

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 can be re-screened if he/she has not been randomized.

Data to be 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 of the patient

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: 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 are:

- 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 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 the patient enrolled in the trial;
- At the discretion of the investigator if the patient safety or well-being is not compatible with trial continuation;
- Screen failure or premature discontinuation of patient due to Covid-19;
- Other reason (to be specified in eCRF).

10.5 Enrolment of additional patient/ healthy volunteer/subject:

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

Tabulations of quantitative parameters will include the following summary statistics: Number of Patients / Mean / Standard Deviation (SD) / Minimum / Median / Maximum. The mean and median will be reported to 1 decimal more than the data; SD to 2 more decimals than the data; and minimum and maximum to the same number of decimals as the data.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group. Percentages will be rounded to one decimal place.

The primary objective of the trial is to demonstrate the non-inferiority of DSC MRI perfusion using Elucirem® at 0.05 mmol/kg compared to DSC-MRI perfusion using Dotarem® at 0.1 mmol/kg in terms of diagnostic quality of the Cerebral Blood Volume (CBV) perfusion map.

From a clinical perspective, a 12% non-inferiority margin was not considered importantly different on diagnostic quality of contrast agents, therefore it is relevant to establish acceptable diagnostic quality of Elucirem® relative to Dotarem®.

The statistical hypotheses are the followings:

- H0: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} \leq -0.12$
- H1: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} > -0.12$

Non-inferiority will be evaluated by testing whether the lower bound of the two-sided Confidence Interval (CI) for the difference of "Elucirem®– Dotarem®", in proportion of patients presenting with images of excellent and good quality according to off-site readers, excludes a 12% difference.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

An interim analysis, on the primary evaluation criterion, is planned. It will be performed when 50% of the patients will be assessed, by the off-site readers, in terms of diagnostic quality of images.

11.2 Sample Size

Sample sizes of 62 in each arm achieve 80% power to detect a difference of 0 when the non-inferiority difference is -0,12. The reference group proportion is 94% [17]. The treatment group proportion is assumed to be 82% under the null hypothesis. The power was computed for the case when the actual treatment group proportion is 94%. The test statistic used is the one-sided Z test (unpooled). The significance level of the test is 2.5% (unilateral, 5% bilateral).

Assuming a 10% drop-out rate is expected, the sample size increases to 138 patients to test that the proportion of patients presenting with images of excellent and good quality in the Elucirem® arm is not inferior to the proportion of patients presenting with images of excellent and good quality in the Dotarem® arm.

The calculations for determine the sample size were performed using the PASS statistical software.

11.3 Planned Analysis

11.3.1 *Disposition of patients/ healthy volunteers/subjects*

Patient disposition will be based on all patients who have signed their informed consent form (ICF) and tabulated, by arm and overall for the following categories:

- Number of patients in each Data Set (see section 11.3.2),
- Total number of patients screened (only overall),
- Number (percentage) of patients randomized,
- Number (percentage) of injected patients,
- Number (percentage) of patients completing the trial,
- Number (percentage) of patients by trial visit,
- Number (percentage) of patients by country and by site,
- Number (percentage) of patients screen failed (only overall) and prematurely discontinued from the trial,
- Reason for screen failure (only overall) and premature discontinuation.

11.3.2 *Data Sets Analyzed*

The patient sets for this trial, will be presented by arm and overall, and are defined below:

- Screened Patients Set (SPS) will include all patients having signed the inform consent form,
- All Randomized Patients Set (ARPS) will include all patients having signed the inform consent form and randomized in the trial,
- Full Analysis Set (FAS) will include all patients who have a valid primary criterion assessment, that is to say images available and considered as technically adequate. Patients will be analysed according to the treatment arm assigned at randomization,
- Per-Protocol Set (PPS) will include all patients from the FAS who have no major protocol deviations and who have complied with the treatment allocated at randomization,
- Safety Set (SS) will include all patients having received at least one injection of IMP regardless of the quantity. Patients will be analysed according to the treatment really received.

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 subject safety or the efficacy assessments.

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

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, naive or recurrent primary glial tumor and/or tumor grade are not available in patients' medical records.
- Imaging protocol not respected with major impact on primary criterion

Other 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 SAP.

11.3.4 *Demographics and Baseline Characteristics*

Demographics and baseline characteristics will be displayed by arm and overall, on the PPS and the FAS unless otherwise specify.

Demographic parameters are age, sex, race, ethnic origin, result of the urinary pregnancy test for women with childbearing potential and body weight.

Baseline characteristics are type of image procedure to detect the glioma (CT, MRI, Other), primary glial tumor type (naïve, recurrent), grade of the primary glial tumor (low grade, high grade) according to the IWRS data and e-CRF, localization of the tumor, the medical patient's history including current medical conditions, imaging history related to GBCA, concomitant procedures / therapeutic measures and the concomitant treatments.

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age and body weight. Frequency and percentages will be calculated for sex, result of the urinary pregnancy test, patient's medical history characteristics, imaging history related to GBCA, concomitant procedures / therapeutic measures and concomitant treatments.

Patient's medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class (SOC), Preferred Term (PT) and status (concomitant or not).

Patient's concomitant procedures / therapeutic measures will be coded using the MedDRA.

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

Moreover, serum creatinine and eGFR data collected at V1 will be presented by group using the PPS, FAS and SS. Serum creatinine and eGFR data will be analyzed quantitatively. eGFR will be also analyzed qualitatively.

Quantitative analyses will be done by tabulating the raw data.

Qualitative analysis of eGFR will present number of patients with value <30 mL/min/1.73m2, ≥30 and <60 mL/min/1.73m2, ≥60 and <90 mL/min/1.73m2, ≥90 mL/min/1.73m2.

11.3.5 *Compliance*

The number of patients with actual volume of IMPs different from the theoretical one will be presented by arm.

Moreover, the absolute (mL) and relative (%) differences between theoretical and actual volumes of IMPs will be presented by arm.

These analyses will be performed on the PPS and SS and presented by arm.

11.3.6 *Efficacy Analysis*

All efficacy analyses will be done using the efficacy sets (PPS and FAS) and presented by arm.

11.3.6.1 Primary analysis

The primary endpoint of the trial is the proportion of patients presenting with images of excellent and good quality, according to off-site readers, in the Elucirem® and the Dotarem® arm.

At the final analysis, non-inferiority will be assessed by calculating the difference in proportion between Elucirem® and Dotarem® arms, and by constructing a two-sided 95.2% CI around this difference. If the lower bound of the two-sided 95.2% CI is above the pre-stated margin of non-inferiority (-12%), Elucirem® will be declared non-inferior to Dotarem®.

The Wald test statistic with a continuity correction will be used.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, at the final analysis, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

The primary analysis will be performed on the PPS and then on the FAS.

11.3.6.2 Secondary analysis

Additional analyses of the primary criterion

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

For the primary evaluation criterion, intra-reader variability will be studied using the Cohen kappa (κ) statistics. Agreement will be classified according to the value of the Cohen kappa statistics as described in the table below:

Table 4: Agreement according to Cohen kappa (κ) statistics

Cohen kappa statistics	Agreement
< 0.2	Poor agreement
≥ 0.2 – ≤ 0.4	Fair agreement
> 0.4 – ≤ 0.6	Moderate agreement
> 0.6 – ≤ 0.8	Good agreement
> 0.8 – 1.0	Very good agreement

Inter- reader variability at patient level
Inter-reader variability will be evaluated on the whole set of trial patients, since each case will be read by the two independent readers.

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

Secondary criteria

Diagnostic quality of the CBV map according to on-site readers

The same methodology as the one presented for the primary criterion will be applied to diagnostic quality of the CBV map according to the on-site readers.

As diagnostic quality of the CBV map according to on-site readers will not be analyzed at the interim analysis, a two-sided 95% CI will be computed at the final analysis.

Technical adequacy of images (on-site and off-site assessment)

Technical adequacy of images will be tabulated according to the following scale:

- non-diagnostic,
- poor,
- fair,
- good.

For the images that will be evaluated by the on-site and off-site readers, as technically non-diagnostic (artifacts that completely compromise the image interpretability), the major artifacts will be tabulated:

- Movement artifacts,
- T2* artifacts,
- EPI distortion,
- Other, please specify.

Quantification of the relative CBV for differentiating tumor grade (off-site assessment)

The Mann-Whitney U-test will be used to test the difference in rCBV between the two trial arms by tumor grade categorization (high grade on one hand and low grade on the other hand) and between patients with high-grade and low-grade gliomas, within each of the two study arms at the significant level of 5%. The analysis will be performed for off-site readers.

Two analyses will be performed. The first one will consider the gliomas' grade categorization (high-grade versus low-grade) according to the stratification factor used at randomization, the second one will use the tumor grade categorization as per histological results (Standard of Truth) collected during the study.

Categorization as per histological results will be the following:

- Grade 1 and Grade 2 = Low grade,
- Grade 3 and Grade 4 = High grade.

The Benjamini-Hochberg method will be used to account for multiple testing.

Assessment and evaluation of the T2* signal intensity time curve (on-site and off-site assessment)

T2* signal intensity time curve will be visually assessed by on-site and off-site readers for the reliability of the curve in providing sufficient information for diagnosis purpose.

Number and percentage of patients for whom the reliability of the curve provides suffice information will be tabulated by trial arms.

For patients for whom the reliability of the curve provides suffice information, confidence in diagnosis will be presented for each arm using a 5-point scale:

- 1 = nil: very uncertain,
- 2 = poor: uncertain,
- 3 = moderate: moderately certain,
- 4 = high: good certainty,
- 5 = excellent: very certain.

Confidence in diagnosis will be summarized qualitatively and quantitatively by trial arm. The on-site and off-site read outcomes will be separately analyzed.

Assessment and evaluation of the T2* signal intensity time curve (off-site assessment)

Only for off-site readers, FWHM and the maximum signal drop will be compared between the trial arms using a Mann-Whitney U-test.

11.3.7 *Adverse Event*

All AEs will be coded using the MedDRA in force at the time of the data base lock.

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 that is to say Non-Treatment Emergent AEs (NTEAE). The table will be presented overall 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 arm and overall for Treatment Emergent AEs (TEAEs) using the SS. The following variables will be also presented:

- Total number of TEAEs with causal relationship to the IMPs.
- Total number of patients with at least one TEAE with causal relationship to the IMPs.
- Total number of TEAEs leading to interruption of IMPs.
- Total number of patients with at least one TEAE leading to discontinuation of IMPs.

The number and percentage of patients with at least one TEAE will be presented using the SS by arm and overall according to Primary SOC and PT.

The number and percentage of patients with at least one TEAE with causal relationship to the IMPs will be presented using the SS by arm and overall according to Primary SOC and PT.

The number and percentage of patients with at least one TEAE with causal relationship to the procedure will be presented using the SS by arm and overall according to Primary SOC and PT.

The number and percentage of patients with at least one AESI will be presented using the SS by arm and overall according to Primary SOC and PT.

The number and percentage of patients with at least one AESI with causal relationship to the IMPs will be presented using the SS by arm and overall according to Primary SOC and PT.

11.3.8 *Laboratory data*

Not Applicable.

11.3.9 *Other safety observations*

Other safety observations analysis will be done using the SS.

Extent of exposure

Duration between ICF signature and the IMPs administration, time from IMP administration to patient's last contact date, and time from signature of ICF to patient's last contact date will be tabulated by arm.

Volume actually administered, occurrence of overdose (if any), actual injection rate of administration, , power injector used, and injection of saline flush (including volume) will be tabulated by arm.

11.4 Specific Statistical Analytical considerations (not applicable for trial including only descriptive analysis)

11.4.1 *Adjustments for Covariates*

Not applicable.

11.4.2 *Handling of Dropouts or Missing Data*

Not applicable.

11.4.3 *Interim Analyses*

An interim analysis will be performed when 50% of the patients will be assessed by the off-site readers, in terms of diagnostic quality of images.

At the interim analysis, only the primary criterion will be analyzed, that is to say the proportion of patients presenting with images of excellent and good quality, according to off-site readers, in the Elucirem® and the Dotarem® arm.

An adjustment of the Type I error will be performed. The interim analysis will be performed at a significant level of 0.001 (unilateral, 0,002 bilateral) leading to the construction of a two-sided 99.8% CI for the non-inferiority testing. The final analysis will be performed at a significant level of 0.024 (unilateral, 0.048 bilateral) leading to the construction of a two-sided 95.2% CI for the non-inferiority testing.

The study will terminate early (at the interim analysis) if the lower bound of the two-sided 99.8% CI is above the pre-stated margin of noninferiority (-12%) as Elucirem® will be declared non-inferior to Dotarem®. Otherwise, the trial will continue until completion of the recruitment.

The results of the interim analysis may be published before the completion of the recruitment.

11.4.4 *Multicentre Trial*

The number of patients included in each site will be displayed in a disposition table overall and by arm.

11.4.5 *Multiple Comparisons/Multiplicity*

For this trial, there will be one interim efficacy analysis, which will be conducted after 50% of the patients will be assessed, by off-site readers, in terms of diagnostic quality of images. As an interim analysis of the primary endpoint is planned, an adjustment of the Type I error will be performed. The interim analysis will be performed at a significant level of 0.001 (unilateral, 0,002 bilateral). The final analysis will be performed at a significant level of 0.024 (unilateral, 0.048 bilateral).

When considering the testing of the superiority of Elucirem® compared to Dotarem® (after non-inferiority was demonstrated), no adjustment for multiplicity is needed as it is a simple closed testing procedure.

Regarding the quantification of rCBV for differentiating tumor grade, the Benjamini-Hochberg method will be used to account for multiple testing.

11.4.6 *Use of an "Efficacy Subset" of patients/ healthy volunteers/subjects*

As the primary objective is to demonstrate non-inferiority of Elucirem® compared to Dotarem®, the corresponding analysis will be done using the PPS and then will be repeated using the FAS.

11.4.7 *Examination of Subgroups*

Not Applicable.

12 TRIAL COMMITTEES

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

An internal committee will assess efficacy results when the results of the interim analysis will be available. The internal committee is composed as following: clinical project manager, biostatistician, head of global medical affairs and clinical development, head of clinical projects – pharmaceuticals and coordinating investigator if any. Based on the evaluation of the internal committee, the Vice President Development, Medical & Regulatory Affairs may decide to stop prematurely the trial or to continue.

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
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Investigation of Medicinal Products in the Pediatric Population E11 Current Step 4 version dated 20 July 2000 and E11 (R1) Addendum dated 20 July 2017
- 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
- Any applicable local regulation

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 IMPs and administration modalities;
- 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 (or designee) 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 25 years after trial completion. Sites should obtain 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 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, MR images, local lab results, power injector records.
- 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 IMPs 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 eCRF will allow recording of all the data required by the protocol except blinded imaging assessment performed by independent readers entered in an 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 eCRF;
- The consistence between the data in the eCRF and those in the source documents, with the exception of those data recorded directly in the eCRF and considered as source data. For this trial, all on-site reading data can be directly entered into eCRF (i.e., no prior written or electronic record of data).

14.3.2 *Data Reported in the 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 eCRF page), eligibility criteria, and any adverse event (AE). 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 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.

15 PUBLICATIONS RULES

No unpublished data given to the Investigator may be transmitted to a third party without prior approval of Guerbet in writing. The trial data are the exclusive property of Guerbet.

The investigator undertakes to submit to Guerbet any draft articles or papers related to this trial before their submission to the scientific journal review board (within 30 days) or the congress scientific committee (within 10 days).

Guerbet or its designee, shall have the right to require amendments to any such proposed presentation or publication on reasonable grounds including without limitation:

(a) to ensure the accuracy of the presentation or publication;
(b) to ensure that proprietary information is not inadvertently divulged;
(c) to enable intellectual property rights to be secured;
(d) to enable relevant supplementary information to be provided.

The Investigator shall be required to comply with any request to amend or delete any statement in a proposed publication, provided such request is based on any one of (a) to (d) above.

All written or oral papers and publications must have the joint agreement of the investigator and Guerbet.

Guerbet shall not use the Investigator's name in any publication within public domain without prior written information of the investigator.

The Investigator shall not use Guerbet's name in any publication without the prior written permission of Guerbet.

In addition, and according to local regulations, the trial may be registered on local regulatory or public databases by Guerbet.

No direct registration of trial information will be made by the investigator on any database without prior agreement of Guerbet.

16 REFERENCES

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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

Not applicable