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STATISTICAL ANALYSIS PLAN

Efficacy and Safety of gadopiclenol for Central Nervous System (CNS) Magnetic Resonance Imaging (MRI)
Phase III Clinical Trial
The PICTURE trial

SPONSOR	**STATISTICAL ANALYSIS PLAN APPROVAL**
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HISTORY FORM

Version	Date	Reason for change
V1.0	9 July 2019	Initial version
V2.0	9 November 2020	Trial design: addition of more precise description of the design Demographic criteria: addition of Geographic region definition and precision of the Medical History and Concomitant Disease coding Secondary Efficacy criteria: clarification in the formulae of LBR General considerations: addition of a statement regarding ICH E9 (R1) handling, precision of ITT principle for efficacy analysis and derivation for time to event Handling of missing data: precision of the rules for imputing missing dates Examination of subgroup: addition of subgroup analysis by magnetic field (1.5tesla and 3tesla) Disposition of patients: precision of the analyzed set used and further description of analyses Disposition of patients: handling of potential premature withdrawal due to COVID pandemic Deviations: update of definition wording and status Deviations: handling of potential deviation due to COVID pandemic Datasets analyzed: Addition of 3 datasets for efficacy analysis and precision of the presentation Efficacy: secondary analysis of the primary criteria updates for intra and inter analyses, clarification that analyses are performed using FAS1 and FAS2 Efficacy: secondary analysis of the primary criteria: addition of global analysis with all readers in the same model and of analysis with non-matching lesion included as well Efficacy: secondary analysis: patient's treatment plan: addition of an analysis with the nature (non malignant/ malignant/not assessable) of the diagnosis done at unenhanced MRI as covariate Efficacy: secondary analysis: patient's treatment plan: descriptive statistics on therapeutic management based on unenhanced MRI in addition of those on therapeutic management based on combined unenhanced and enhanced MRI Exposure: addition of two periods for description, from informed consent signed to 1st IMP injection and from informed consent signed to end of trial Safety: Clinical laboratory evaluation: precision of unit for laboratory parameters Safety: Clinical laboratory evaluation: description of derivation of urea parameter from blood urea nitrogen Safety: Clinical laboratory evaluation: correction of classification of eGFR, creatinine, BUN at baseline for shift tables

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Amino Transferase
ANOVA	ANalysis Of VAriance
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
BMI	Body Mass Index
BW	Body Weight
CA	Competent Authority
CI	Confidence Interval
CNR	Contrast to Noise Ratio
CNS	Central Nervous System
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
E%	Percentage enhancement of lesion
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBCA	Gadolinium Based Contrast Agent
HLGT	High-Level Group Term
HLT	High-Level Term
IBR	Independent Blinded Reader
ICC	Intra Class Correlation
ICH	International Conference on Harmonization
ICF	Inform Consent Form
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
LBR	Lesion to Background Ratio
LDH	Lactate Dehydrogenase
LLT	Lower Level term
MCV	Mean red blood Cells Volume
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance imaging
NTEAE	Non-Treatment Emergent AE
PPS	Per Protocol Set
PT	Preferred Term
RBCs	Red Blood Cells
SAE	Serious Adverse event
SAP	Statistical Analysis Plan
SS	Safety Set
SD	Standard Deviation
SI	Signal Intensity
SOC	System Organ Classes

SPS	Screened Patient Set
TEAE	Treatment Emergent Adverse Event
WBCs	White Blood Cells
WHO-DD	World Harmonization Organization-Dictionary Drug

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1. SUMMARY OF THE TRIAL PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet Protocol No. GDX-04-010: "Efficacy and Safety of gadopiclenol for Central Nervous System (CNS) Magnetic Resonance Imaging (MRI)".

This analysis plan is based on the final protocol Version 1.0 dated December 20, 2018 and the amendment for FRANCE dated June 4, 2019.

1.1. Trial objectives

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

1.1.1. Primary objectives

Primary objective 1:

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

Primary objective 2:

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

For Food and Drug Administration (FDA), the primary objective 1 is to be achieved. The primary objective 2 will serve as one of the secondary objectives.

For European Medicine Agency (EMA), both primary objectives 1 and 2 are to be achieved.

1.1.2. Secondary Objectives

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

- ✓ Lesion to Background Ratio (LBR)
- ✓ Overall diagnostic preference

- To assess the safety profile of gadopiclenol and gadobutrol

1.2. Trial design

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

The Investigational Medicinal Products (IMPs) used during the trial are gadopiclenol and gadobutrol.
Patients will perform a screening visit (V1) to confirm trial eligibility, then will be randomized in the trial to determine the order of IMP injection. The randomization scheme will allocate patients in a 1:1 ratio to the two series, gadopiclenol-gadobutrol or gadobutrol-gadopiclenol. Each of the 2 MRI visits (V2 and V4) will be followed by a safety visit (V3 and V5) performed 1 day after the MRI visit.
Images will be evaluated by prospective evaluation of the blinded images in a centralized and blinded manner. The blinded image evaluations (off-site read) will be performed by 3 independent blinded radiologists for the reading of random images and by 3 additional independent blinded radiologists for the global pairs assessment.

2. EVALUATION CRITERIA

2.1. Demographic, other baseline characteristics and MRI examination

Demographic parameters are age, sex, race, ethnic data, childbearing potential, body weight, height and body mass index (BMI) and geographic regions.

BMI is calculated as follow: $BMI = \frac{BodyWeight(Kg)}{Height(m)^2}$

Age will be categorized as follow: <65 and ≥65 years

Country will be categorized in Geographic regions as follow:

- United States of America: North America
- Mexico: Latin America
- Republic of Korea and Taiwan: Asia Pacific
- Hungary, France, Spain, Italy, Poland, Belgium, Germany: European countries

Other baseline characteristics are

- Imaging procedure documenting the trial disease
- Trial disease
- Estimated Glomerular Filtration rate (eGFR)
- Medical history and concomitant diseases
- Patient intolerance history related to contrast agent
- Prior medications
- MRI examination parameters.

Trial disease diagnosis will be coded in System Organ Classes (SOC) and preferred terms (PT) using the MedDRA v23.1 - Sep 2020.
Medical history and concomitant diseases will be coded in SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) v23.1 - Sep 2020 dictionary. Medical histories are the ones flagged as "Not Ongoing" and concomitant diseases are those flagged as "Ongoing" at the screening visit.
Prior medications are defined as medications ended before the first administration and will be coded using the B3 WHO Drug Global - Sep 2020.
MRI examination parameters are:

- MRI machine manufacturer name
- MRI machine field strength in tesla (1.5 or 3.0)
- MRI examination (Brain or Spine)

2.2. Efficacy criteria

2.2.1. Primary criteria

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

The lesion visualization assessment is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement assessed on the images acquired during the MRI performed with gadopiclenol.
Each Independent Blinded Readers (IBR) will record each of the 3 co-primary criteria for up to 3 most representative lesions, on Paired images (contrast-enhanced + unenhanced images) versus Pre-contrast images (unenhanced images) on a 4-point scale as described below:

- **Border delineation:**

Delineation of the lesion border is defined as the distinction of lesion from surrounding tissues, structures, or edema; and the detection of extent of the lesion. This criterion will be assessed through the following scale:

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

- **Internal morphology:**

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

1 = Poor: poorly seen
2 = Moderate: majority of lesion is poorly seen but with minor parts of lesion visible
3 = Good: majority of lesion is clearly seen but with minor parts of lesion invisible
4 = Excellent: lesion is well seen and can see "through" lesion to observe any complex areas of necrosis or hemorrhage or cyst formation

- **Degree of contrast enhancement:**

This criterion is a qualitative assessment (not based on signal intensity measurement) according to the following scale:

1 = No: no enhancement
2 = Moderate: weakly enhanced
3 = Good: clearly enhanced
4 = Excellent: clearly and brightly enhanced

The mean score for each of the 3 lesion visualization co-primary criteria will be calculated as follows:
Mean score = (score of the lesion 1 + score of the lesion 2 (if any) + score of the lesion 3 (if any)) divided by the number of lesions (up to 3 most representative lesions).

For each reader, only matching lesions between Paired images with gadopiclenol and Pre-contrast images will be considered for the evaluation of the primary criteria 1.

For each reader, if the Magnetic Resonance (MR) images are not assessable or if no matching lesion between Paired images with gadopiclenol and Pre-contrast images is identified, then the patient will not be included in the evaluation of primary criteria 1.
The mean score for each co-primary criterion of the lesion visualization will range from 1 to 4.

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

The same 3 co-primary criteria of lesion visualization: border delineation, internal morphology and degree of contrast enhancement, will be assessed on the images acquired during the MRI performed with gadopiclenol and those performed with gadobutrol.
The IBR will record each of the 3 co-primary criteria for up to 3 most representative lesions, on Paired images performed with gadopiclenol and Paired images performed with gadobutrol using a 4-point scale.
Definitions of each co-primary criteria and score calculation are provided in primary criteria 1 description.

For each reader, only matching lesion on paired images between gadopiclenol and gadobutrol will be considered for the evaluation of the primary criteria 2.
For each reader, if the MR images are not assessable or if no matching lesion on Paired images between gadopiclenol and gadobutrol is identified, then the patient will not be included in the evaluation of primary criteria 2.
The mean score for each co-primary criterion of the lesion visualization will range from 1 to 4.

2.2.2. Secondary efficacy Criteria

- Primary criteria 2 is considered as secondary for FDA.

- Lesion visualization at lesion level (off-site read)
  The same 3 co-primary criteria of lesion visualization: border delineation, internal morphology and degree of contrast enhancement, will be assessed on the images acquired during the MRI performed with gadopiclenol and those performed with gadobutrol.
  The IBR will record each of the 3 co-primary criteria for up to 3 most representative lesions, on Paired images performed with gadopiclenol and Paired images performed with gadobutrol using a 4-point scale.
  Definitions of each co-primary criterion are provided in primary criteria 1 description.

- Lesion visualization (on-site read)
  The lesion visualization (on-site read) criteria are based on 3 co-primary criteria assessed by the investigator for each contrast agent on Pre-contrast and Paired images. The 3 co-primary criteria definition is presented in section 2.2.1. No lesion matching will be performed for on-site read.
  The mean score for each of the 3 lesion visualization criteria will be calculated as follows:
  Mean score = (score of the lesion 1 + score of the lesion 2 (if any) + score of the lesion 3 (if any)) divided by the number of lesions (up to 3 most representative lesions).

- Improvement in patient lesion visualization scores, paired versus pre-contrast images (on-site and off-site read)
  The lesion visualization criteria and the mean score calculation are presented in section 2.2.1. For each contrast agent for the 3 co-primary criteria, the mean score is calculated and compared between Pre-contrast and Paired images:
  - If the mean score of Paired images is greater than those of Pre-contrast images, then the Paired image will be classified as “Better”;

- If the mean score of Paired images is equal or less than those of Pre-contrast images, then the Paired image will be classified as "Not Better".

- Technical adequacy of images (on-site and off-site read)
  For each contrast agent, images will be evaluated as technically adequate for diagnosis on a 4-point scale and as assessable or not by investigators and IBR.
  The technical adequacy of images will be rated on a 4-point scale:
  1 = Non diagnostic
  2 = Poor
  3 = Fair
  4 = Good
  Images should be evaluated as assessable or not and if not, the reasons should be recorded:
  1 = Artifacts due to patient
  2 = Artifacts due to machine
  3 = Injection technical failure
  4 = Inadequate anatomic coverage
  5 = Other, specify

- Number, size and location of lesions (on-site and off-site read)
  Number and location of lesions is assessed for each contrast agent on Pre-contrast and Paired images.
  The largest diameter of the 3 most representative lesion will be recorded.

- Diagnostic confidence (on-site and off-site read)
  The investigator/IBR will record in the electronic Case Report form (eCRF) his/her diagnosis (malignant lesion, or if not assessable) and his/her confidence in diagnosis for Pre contrast and Paired images of each contrast agent.
  Degree of confidence for each contrast agent will be assessed using a 5 point-scale
  1 = nil: very uncertain
  2 = poor: uncertain
  3 = moderate: moderately certain
  4 = high: good certainty
  5 = excellent: very certain

- Impact of contrast-enhanced MRI on patient treatment plan (on-site)
  The impact of contrast-enhanced MRI on patient treatment plan is assessed for each contrast agent by the fact whether the patient treatment plan as changed based on the images obtained (yes/no). If yes, the therapeutic management proposed based on radiological assessment is as the following:
  - Surgery
  - Biopsy
  - Chemotherapy
  - Radiotherapy
  - Other treatment: specify

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

- Contrast to Noise ratio (CNR)

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

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

- Percentage enhancement (E%) of lesion

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

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

- Lesion to Background Ratio (LBR)

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

where SI_{lesion} = Signal intensity of lesion
SI_{ht} = Signal intensity of healthy tissue (brain or spinal cord)

- Overall diagnostic preference (off-site read)
The evaluation will be performed in a global matched-pairs fashion and preference will be determine on a 3-point scale:
  - 1: for when examination 1 is preferred to examination 2
  - 0: for when no preference is observed
  - 2: for when examination 2 is preferred to examination 1

  Reason for preference will also be recorded according to the following:
  - Contrast enhancement was superior,
  - Delineation of normal structure was better
  - Delineation of at least one lesion was better
  - Internal structure of lesions was better visualized
  - More lesions were identified
  - Diagnostic confidence was greater (specify one or more reason(s): detection of lesions, characterization of disease, assignment of a grade to disease, definition of extent of disease, or other reasons that had to be specified on the eCRF)

2.3. Safety criteria

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

- **Vital signs**

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

- prior to each contrast agent injection (baseline value is the last measurement prior to the first agent injection)
- At 60 ± 15 minutes following each contrast agent injection
- One day after each contrast injection

- **Injection-site tolerance**

Injection-site tolerance (pain, eruption, extravasation, inflammation, or other) will be assessed over 1 day following each contrast injection (during the injection, 60 min ± 15 min post injection and the day after injection) and over a longer period if the investigator becomes aware of any related AE. In case of injection-site pain, the patient will be asked to specify the level of pain using a Numeric Pain intensity Scale from 0 (no pain) to 10 (maximal pain).

- **Local laboratory parameters**

Serum creatinine and Estimated Glomerular Filtration Rate (eGFR) will be collected according to the following schedules:

- prior to each contrast agent injection (baseline value is samples collected prior to the first agent injection)
- one day after each contrast injection.

- **Central laboratory parameters**

Measurements below or above the limit of quantification will be imputed to the limit for quantitative analyses. They will remain as provided by the laboratory in listings.

Blood samples will be collected according to the following schedules:

- prior to each contrast agent injection (baseline value is samples collected prior to the first agent injection)
- one day after each contrast injection

The following parameters will be obtained and assessed centrally:

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

- **Adverse events**

Adverse Events will be recorded throughout patient's participation. AEs will be coded using the MedDRA v23.1 - Sep 2020 dictionary.

- **Procedure related to a reported AE**

Concomitant procedures are defined as procedure related to a reported AE, even if the procedure has ended before the first administration of IMP. Procedure will be recorded throughout patient's participation and will be coded using the MedDRA v23.1 - Sep 2020 dictionary.

- **Concomitant medications**

Concomitant medications are defined as those ongoing at or started after the first contrast agent administration and will be coded using the B3 WHO Drug Global - Sep 2020.

3. STATISTICAL METHODS

3.1. General considerations

With regards to the ICH topic E9 addendum, it has been decided to not use the wording estimand. Indeed, the protocol was drafted in 2018 when the addendum was not yet adopted by competent authorities (CA). Nevertheless, for this diagnostic cross-over study, all analyses and presentation asked by CA in this addendum were considered and put in place if needed. Hence, no strategy for dealing with intercurrent event is considered. However, sensitivity analyses are planned in order to assess the robustness of the primary analysis. As it is expected that very few patients will drop-out because of diagnostic results of first period but rather for safety, consent withdrawal or technical reasons, no specific missing data handling is planned. However, a sensitivity analysis accounting for discontinued patient is planned (in the mixed models).

After the database lock, the statistical analysis will be performed by a Contract Research Organization (CRO[redacted]) under the supervision of Guerbet biostatistician, on the basis of the present document.

A quality control of the statistical analysis will be performed by the CRO to ensure the reliability of the results prior to providing the results to Guerbet.

Some analyses will be presented by series (gadopiclenol-gadobutrol / gadobutrol- gadopiclenol), especially those about demographic and baseline characteristics. Some analyses will be presented by MR modality (pre /paired) and some by contrast agent group (gadopiclenol / gadobutrol), especially those in efficacy and safety. For the presentation by contrast agent group, efficacy analyses will be presented as randomized that is to say presented by allocated contrast media whereas safety analyses will be presented by actually administered contrast media.

Tabulations of quantitative parameters will include the following summary statistics: Number of Patients / Mean / Standard Deviation / Minimum / Median / Maximum and number of missing data if any. If for a given parameter, the raw value has been collected with x decimal places, the mean, median and standard deviation will be rounded to x+1 decimal places, while the minimum and maximum values will be tabulated as reported with x decimal places.

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 category missing will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing recorded categories.

For the safety evaluation, the **baseline value** will be defined as the last available value prior to the first administration of any investigational product.

Duration between two dates will be calculated as follow: date 2 – date 1 + 1
Time to event from date 1 will be calculated as follow: date of event – date 1.

SAS® version 9.4 will be used for all descriptive summaries and inferential analyses.

3.2. Null and alternative hypothesis

For FDA, the primary objective 1 is to be achieved for at least two readers out of three.
For EMA, both primary objectives 1 and 2 are to be achieved for at least two readers out of three.

Primary objective 1

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

The alternative hypothesis is that the difference in mean scores between Paired images and Pre-contrast images for each of the 3 co-primary criteria is greater than 0.
That is to say if μ is the expected mean of the patient score (within patient difference ["Paired" scores mean – "Pre" scores mean]) for each of co-primary criteria in the gadopiclenol group:

Null hypothesis H_0: $\mu = 0$
Alternative hypothesis H_1: $\mu > 0$
Statistical Test: T-Test for paired observations

Decision Criterion: The mean of patients score is calculated for each reader. The Null hypothesis is rejected if the difference – "Paired" score minus "Pre" score - is significantly different from zero with a type 1 error set at 0.025.
To conclude that gadopiclenol-enhanced MRI is greater than unenhanced MRI, the null hypothesis has to be rejected for all co-criteria simultaneously.

Primary objective 2

- Non-inferiority margin:

For EMA, both primary objectives 1 and 2 are to be achieved. With primary objective 1, this trial will provide a direct demonstration of the superiority of gadopiclenol images over unenhanced images. It can be considered as three-armed trial design with unenhanced images as placebo as described in *EMA guideline on the choice of the non-inferiority margin* (below). As such, it is not necessary to define a value for non-inferiority margin to establish that gadopiclenol has efficacy and the non-inferiority margin is only based on clinically relevance.
A 10% non-inferiority margin was considered clinically as an unimportant difference and therefore relevant to establish acceptable efficacy relative to gadobutrol (objective 2). Based on the Guerbet Phase IIb GDX-44-004 clinical trial results of lesion visualization criteria, the mean score for each of the 3 co-criteria is expected to be equal to 3.5, so the margin is set to 0.35 (10%).

- Hypotheses:

The null hypothesis is that the difference in mean scores between gadopiclenol and gadobutrol for each of the 3 primary criteria is equal to the non inferiority margin.
The alternative hypothesis is that the difference in mean scores between gadopiclenol and gadobutrol for each of the 3 primary criteria is greater than the non inferiority margin.
That is to say if μ is the expected mean of the patient score (within patient difference [gadopiclenol scores mean – gadobutrol scores mean]).

Null hypothesis H_0: $\mu = -0.35$
Alternative hypothesis H_1: $\mu > -0.35$
Statistical Test: T-Test for paired observations

Decision Criterion: The mean of patients score is calculated for each reader. The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference – gadopiclenol score minus gadobutrol score - had its lower limit above -0.35.

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

3.3. Determination of sample size

The sample size assessment was performed by a CRO [redacted] using software PASS version 15.0.4.

Number of patients for the Primary objective 1:
The success hypothesis used in the sample calculation is based upon the Gutierrez publication (below) where the minimal observed mean of the difference was 0.41 with a SD ranging from 0.5 to 0.8 as displayed below.

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

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

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

Hence, expecting that for each of the 3 co-primary criteria, the difference in mean scores will be 0.35 (["Paired" – "Pre"] within patient) with 1.5 standard deviation, a sample of 200 patients in the gadopiclenol group will have 90% power when using a single group superiority t-test with a 0.025 one-sided significance level.
As a 20% drop-out rate is expected, sample size increases to 250 patients.

Number of patients for the primary objective 2:

- Sample size hypothesis:

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

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

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

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

For this 2x2 cross-over design, the statistical analysis is based on the observed Student's t-based two-sided 95%CI of the gadopiclenol-gadobutrol difference for each co-primary criterion. An enrollment of 200 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin set to 0.35. Assuming 80% power and for each co-primary criterion, the expected difference in mean scores is 0 with an expected standard deviation of 1.75.
If one assumed a patient drop-out rate of 20%, a minimum enrollment of 250 patients with CNS lesions is planned.
Therefore, a total number of 250 patients will allow a sufficient power to meet both objectives.

3.4. Adjustment for covariates

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

3.5. Handling of dropouts or missing data

3.5.1. **Efficacy Analyses**

No imputation will be performed in this study.

3.5.2. **Missing and Partially Known Dates (Except AE Start Dates)**

Unless otherwise specified, partially known dates will be defined as follows for duration computation:

Partially known start date
If only the day is missing, it is estimated as the first day of the month or day of the first date in the study if it is the same month and year.
If month and day are missing, they are estimated as January 1 or day and month of the first date in the study if it is the same year.

Partially known end date
If only the day is missing, it is estimated as the last day of the month or day of the last date in the study if it is the same month and year.
If month and day are missing, they are estimated as December 31 or day and month of the last date in the study if it is the same year.

The original dates without estimation will be presented in the listings.

General rules for calculating the durations

- Durations calculated in minutes: if any one of the times from the start and end "datetimes" used for the calculation of the duration is/are missing, the duration is missing.
- Durations calculated in days: if any one of the times from the start and end "datetimes" used for the calculation is/are missing, the date part of the datetime will be used to compute the duration.

3.5.3. **Missing and Partially Known AE Start Dates**

If an AE start date is missing or unknown, the AE will be considered as treatment emergent.

When the start date of an AE is only partially known, it will be categorized as not emergent or emergent using the following rules:

- If the partial start date is before (<) the injection at the 1st MRI procedure visit date (i.e., year or year & month is/are before those of the date of the injection) then the AE is not emergent.
- If the partial start date is after (≥) the injection at the 1st MRI procedure visit date (i.e., year or year & month is/are the same as or after those of the date injection) then the AE is emergent.

3.5.4. **Missing data for Start or End Date of Concomitant Medication or Procedure**

In case of missing data for start or end date of a concomitant medication, it will be imputed so that the medication will be considered as concomitant. Hence, as no time for concomitant procedure is collected, if the procedure is undergone the same day of the contrast agent administration then the procedure will be considered as being after the contrast agent administered that day.

3.6. Interim analyses and data monitoring

No interim analysis is planned.

3.7. Multicenter studies

As a high number of centers is expected for this trial, the center factor will not be included in the models for efficacy except for the analysis at lesion level for which the number of observations and so the degree of freedom is deemed sufficient. The number of patients screened in each center will be displayed in a disposition table.

3.8. Multiple comparisons/Multiplicity

For FDA, the primary objective 1 is to be achieved. The primary objective 2 will serve as one of the secondary objectives.
For EMA, both primary objectives 1 and 2 are to be achieved.
Therefore, no multiplicity adjustment is needed for this trial as only one objective should be reached for FDA and the two primary objectives should be reached simultaneously for EMA.
Furthermore, each objective (superiority of Paired vs Pre, and non-inferiority of the two contrast agents), will be considered achieved only if the null hypothesis is rejected for the 3 co-primary criteria simultaneously for at least two readers out of three. Results for each reader will be analyzed separately.

3.9. Use of an "efficacy subset"

As the primary objective 1 is superiority, the corresponding analysis will be done using the Full Analysis Set and then the analysis repeated using the Per Protocol Set.
As the primary objective 2 is non-inferiority, the corresponding analysis will be done using the Per Protocol Set and then the analysis will be repeated using the Full Analysis Set.

3.10. Active control studies intended to show equivalence

Not-applicable.

3.11. Examinations of subgroups

Primary criteria statistics descriptive will be provided by main demographic parameters (age, sex, race, ethnicity and geographic region) and MRI machine field strength.
Sensitivity analyses of the superiority analysis (primary criteria 1) and of the non-inferiority analysis (primary criteria 2) will be conducted using the same linear model with demographic parameters and MRI machine field as additional factors.

4. CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

Three additional datasets will be defined and used for additional secondary efficacy analyses.

Four supplemental secondary analyses of lesion visualization criteria will be conducted in addition of those described in the final protocol Version 1.0 dated December 20, 2018 and the amendment for FRANCE dated June 4, 2019.

- An analysis will be performed globally putting together all off-site readers. Mixed model will be considered with patient and off site reader as adjustment factors.
- An analysis will be performed including non-matching lesions. Mixed model will be considered by off site reader with patient as adjustment factor.
- An analysis will be performed at lesion level. Mixed model will be considered by off site reader with patient and center as adjustment factors.
- Subgroup analysis will be performed considering main demographic parameters (age, sex, race, ethnicity and geographic region) and MRI machine field (1.5 tesla and 3 tesla) for the 3 co-primary criteria.

In addition, if the number of patients dropping out is different between series, non-inferiority analysis will be repeated on all patients having at least one MRI performed.

Two analyses of the secondary criterion “patient’s treatment plan” will be added: presentation of the results according to diagnosis (non-malignant/malignant/not assessable) done at unenhanced MRI and addition of therapeutic management based on unenhanced MRI.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of patients

All following analyses will be presented on Screened Patients Set defined by all patients having signed the inform consent form.
Number of patients undergoing each visit will be presented by series and overall.
The overall disposition (number of screened patients, randomized patients, patients having received the first contrast agent administration, having received the second agent administration, and patients who completed the trial) will be presented by series and overall. The reason of screen failure for not randomized patients will be presented overall and the reason of premature discontinuation for randomized patients will be presented by series and overall, by period (before receiving the first contrast agent, before receiving the second contrast agent and after receiving the second contrast agent separately).
If a patient withdraws for Adverse Event (AE) and at least one AE is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at COVID-19 but if no AE is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at AE other than COVID-19
If a patient withdraws for "other" reason, then the reason of premature withdrawal will be derived from the specified field as the following:

Specified field	Reason of premature withdrawal
"COVID-19 crisis preventing patient to follow protocol schedule"	COVID-19 pandemic preventing patient to follow protocol schedule
"Withdrawal of patient's consent due to Covid-19 crisis"	Withdrawal of patient's consent due to Covid-19 pandemic
Other	Other reason

Number of patients by country and center will be presented overall as well.

5.2. Data Sets Analysed and protocol deviations

Data sets analysed
There will be nine patient sets defined for this trial:

- Screened patients Set (SPS) will include all patients having signed the inform consent form
- Safety Set (SS) will include all patients having received at least one injection of Investigational Medicinal Product (IMP) regardless of the quantity
- All Randomized Set (ARS) will include all patients having performed at least one MRI examination with injection of IMP.
- Extended_FAS1 will include all patients who have both gadopiclenol pre contrast and paired images assessable
- Extended FAS2 will include all patients who have both gadopiclenol and gadobutrol paired images assessable
- Full Analysis Set (FAS) will include all patients who have a valid primary criterion assessment
    - FAS1 will include all patients who have both pre and paired images with gadopiclenol assessable for primary criteria 1 for at least one matching lesion for at least one off-site reader
    - FAS2 will include all patients who have paired images for both gadopiclenol and gadobutrol assessable for primary criteria 2 for at least one matching lesion for at least one off-site reader
- Per-Protocol Set (PPS) will include all patients who have no major protocol deviations and a valid primary criterion assessment:

- PPS1 will include all patients from the FAS1 who have no major protocol deviations for primary criteria 1
- PPS2 will include all patients from the FAS2 who have no major protocol deviations for primary criteria 2

Analyses Sets	Screened patients Set	Safety Set	All Rando-mized Set	Extended Full Analysis Set		Full Analysis Set		Per Protocol Set	
				Extended FAS1	Extende dFAS2	FAS1	FAS2	PPS1	PPS2
Disposition	✓								
Protocol deviations	✓								
Demographics and Population characteristics		✓				✓	✓		
Compliance						✓	✓		
Efficacy evaluation: primary analysis of primary criteria 1						✓			
Efficacy evaluation: primary analysis of primary criteria 2									✓
Efficacy evaluation: secondary analysis of primary criteria 1				✓		✓		✓	
Efficacy evaluation: secondary analysis of primary criteria 2			✓		✓		✓		
Efficacy evaluation: Secondary criteria			✓	✓	✓	✓	✓		
Safety evaluation		✓							

The use of the PPS in the non-inferiority analysis will maximize the opportunity for both contrast agent to show the efficacy under the intended scientific model of the protocol. Indeed, there is a risk that poor compliance in both contrast agent groups would lead to similar outcomes from the two groups in the FAS.

Protocol deviations

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

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

If the reason of deviations is related to the COVID 19 pandemic then it will be specified in the Statistical Review Meeting Minutes and the corresponding deviation presented apart

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 criteria 1 or primary criteria 2. The initial categorization is proposed in this document, the final categorization will be performed before breaking the blind. The decision will be duly described in the meeting minutes.

The deviations are listed in the table below:

Category	Description	Source	Status
Inclusion criteria not met/ Non inclusion criteria met	Inclusion criteria n°6 not met: Patient not having read the information or not having provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted	Clinical data base	**Major**
	Non inclusion criteria n°1 met: Patient presenting extra cranial lesions and/or extra-dural lesions	Clinical data base	**Major**
	Non inclusion criteria n°7 met: Patient having received any contrast agent (MRI or CT) within 3 days prior to first trial product administration, or scheduled to receive any contrast agent during the course of the trial or within 24 hours after the second trial product administration	Clinical data base	Non major
	Patient having received any MRI contrast agent within 3 days prior to each product administration,	Monitoring	**Major primary criteria2**
	At least one inclusion criteria except n°6 not met	Clinical data base	Non major
	At least one non -inclusion criteria except n°1 and n°7 met	Clinical data base	Non major
	eGFR at visit 2 or visit 4 below 30 mL/min/1.73m^2 and contrast agent administration performed	Clinical data base	Non major
	eGFR not measured within one day before contrast agent administration	Clinical data base	Non major
	eGFR measurement at visit 2 or visit 4 is missing	Clinical data base	Non major
	eGFR method at visit 2 or visit 4 is not accurate	Clinical data base	Non major
	No pregnancy test done within 1 day before contrast agent administration for female of childbearing potential	Clinical data base	Non major
	Result of pregnancy test positive and contrast agent administration performed	Clinical data base	Non major
Trial disease	Procedure used for detecting the trial disease is **not** provided	Clinical data base	Non major
	Procedure used for detecting the trial disease is not performed within 12 months prior to ICF signature	Clinical data base	Non major
Imaging	Not matching lesion: among patients with gadopiclenol MRI examination available, those with no **matching enhancing** lesions on paired and pre-contrast images for all off-site readers	Imaging data base	**Major primary criteria1**
	Not matching lesion: among patients with both MRI examinations available, those with no **matching enhancing** lesions at both examination for all off-site readers	Imaging data base	**Major primary criteria2**
	Imaging protocol not respected with major impact on co-primary criteria for gadopiclenol administration	Monitoring	**Major**

Category	Description	Source	Status
	Imaging protocol not respected with major impact on co-primary criteria for gadobutrol administration	Monitoring	**Major primary criteria2**
	Imaging protocol not respected with non-major impact on primary criterion	Monitoring	Non major
Unblinding	Blind not maintained on site	Monitoring	Non major
	Blind not maintained at central reading level	Monitoring	**Major**
Forbidden concomitant medication	Concomitant medication or medical procedure taken between the two MRI significantly impacting lesion size and its enhancement pattern	Clinical data base	**Major primary criteria2**
IMP deviation	Patient does not receive the IMP allocated by randomization	Clinical data base and IWRS data base	**Major**
	Patient having performed MRI examination but **not** administered with gadopiclenol	Clinical data base	**Major**
	Patient having performed MRI examination but **not** administered with gadobutrol	Clinical data base	**Major primary criteria2**
	The gadopiclenol volume actually administered is different from the theoretical one from 10 to 20%	Clinical data base and IWRS data base	Non major
	The gadobutrol volume actually administered is different from the theoretical one from 10 to 20%	Clinical data base and IWRS data base	Non major
	The gadopiclenol volume actually administered is different from the theoretical one more than 20%	Clinical data base and IWRS	**Major**
	The gadobutrol volume actually administered is different from the theoretical one more than 20%	Clinical data base and IWRS	**Major primary criteria2**
	Actual IMP injection rate is **not** adequate	Clinical data base	Non major
	Temperature excursion for IMP	Monitoring	Non major
	IMP management not appropriate	Monitoring	Non major
	Suspicion of Lack of efficacy for gadopiclenol	Monitoring	**major**
	Suspicion of Lack of efficacy for gadobutrol	Monitoring	**Major primary criteria2**
	Extravasation during gadopiclenol administration	Clinical data base	**Major**
	Extravasation during gadobutrol administration	Clinical data base	**Major primary criteria2**
	Saline flush not done after IMP administration manually	Clinical data base	Non major
	Saline flush not done after IMP administration by power injector	Clinical data base	Non major
Missing data	Age is missing	Clinical data base	Non major
	Sex is missing	Clinical data base	Non major
	Weight is missing	Clinical data base	Non major
	Height is missing	Clinical data base	Non major

Category	Description	Source	Status
	Ethnicity is missing	Clinical data base	Non major
	Race is missing	Clinical data base	Non major
	eGFR measurement at visit 3 or visit 5 is missing	Clinical data base	Non major
	Central Laboratory Biochemistry results **not** available for at least one parameter	Laboratory data base	Non major
	Central Laboratory Hematology results **not** available for at least one parameter	Laboratory data base	Non major
	Vital sign results missing	Clinical data base	Non major
	Tolerance at injection site is not filled in for patient receiving the study product	Clinical data base	Non major
	No Numeric Pain Intensity Scale completed in case of injection site pain	Clinical data base	Non major
Non respect of study's schedule and procedures	MRI examination with gadopiclenol **not** performed	Clinical data base	**Major**
	MRI examination with gadobutrol **not** performed	Clinical data base	**Major primary criteria2**
	Time between the two MRI procedures is strictly greater than 14 days and less or equal to 21 days	Clinical data base	Non major
	Time between the two MRI procedures is strictly less than 2 days and strictly greater than 21 days	Clinical data base	**Major primary criteria2**
	Two different MRI system manufacturer used for both assessments of the same patient	Clinical data base	Non major
	Two different magnetic field strength used for both assessments	Clinical data base	**Major primary criteria2**
	MRI machine used not qualified	Monitoring	Non major
	Physical examination **not** performed	Clinical data base	Non major
	eGFR method is not the same throughout the trial	Monitoring	Non major
	Time between screening visit and first contrast agent administration is strictly greater than 7 days	Clinical data base	Non major
	Blood sample for central laboratory assessment is not drawn in the time window allowed by protocol	Clinical data base/	Non major
	Vital sign is not measured in the time window allowed by protocol	Clinical data base	Non major
	Last contact is not between 7 and 14 days after the last injection of IMP for patients recruited in France	Clinical data base	Non major
	Deviation in IWRS process	Monitoring	Non major
	Additional lab sampling was done out of protocol requirement	Monitoring	Non major
	Patient having received any contrast agent within 24 hours after trial product administration	Monitoring	Non major
GCP deviation	Deviations related to ICF management process	Monitoring	Non major
	Source document management not appropriate	Monitoring	Non major
	Source imaging document management not appropriate	Monitoring	Non major

Category	Description	Source	Status
	Deviation to blind charter in regards to data correction	Monitoring	Non major

Patients presenting at least one protocol deviation with a status "**Major**" will be excluded from the PPS1 and PPS2.
Patients presenting at least one protocol deviation with a status "**Major primary criteria1**" will be excluded from the PPS1.
Patients presenting at least one protocol deviation with a status "**Major primary criteria2**" will be excluded from the PPS2.

Frequency and percentages of patients with protocol deviations will be presented breaking down by status (major/non major).

Patients with major protocol deviations will be presented by series and globally on the Screened Patient Set:
- patients with at least one protocol deviation with a status "**Major**",
- patients with at least one protocol deviation with a status "**Major criteria1**",
- patients with at least one protocol deviation with a status "**Major criteria2**".

Patients with non-major protocol deviations will be presented by serie and globally on the Screened Patient Set as well.

Number of patients in the ARS, extended FAS1, extended FAS2, FAS1, FAS2, PPS1 and PPS2 will be presented by series and overall on Screened Patients Set.
Number of patients in the Safety Set will be presented by contrast agent groups and overall on Screened Patients Set.

5.3. Measurements of trial drug compliance

Compliance with gadopiclenol will be presented using the FAS1 and compliance with each contrast agent group actually received using the FAS2. The number of patients with actual volume of trial product different from, less and greater than the theoretical one will be presented.
Theoretical volume will be calculated by multiplying the body weight measured at the same visit by 0.1 and rounded to the nearest whole number.
The raw (mL) and relative (%) differences between theoretical and actual volumes of trial product will be tabulated for each MR examination.
The raw difference will be calculated as follow: actual volume – theoretical volume.
The relative difference will be calculated as follow: abs (actual volume – theoretical volume) / theoretical volume.
Listing of measurements of compliance with trial drug will be presented in CSR appendix 16.2.5.

5.4. Demographic and Other Baseline Characteristics

5.4.1. Demographic data

Summary statistics for quantitative data will be calculated for age, weight (both at Visit 2 and Visit 4 before each injection), height and BMI. Frequency and percentages will be calculated for age categorized, sex, childbearing potential, race, ethnic origin and geographic regions.
Demographics will be tabulated by series and overall using FAS1, FAS2 and by contrast agent group using Safety set.
Listing of demographics will be presented in CSR Appendix 16.2.4.

5.4.2. Trial disease

Summary tables (number and % of patients) grouped by SOC and PT will be presented by series and overall using FAS1 and FAS2.Tables will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT according the overall population.

Time between imaging procedure documenting the trial disease and first injection of trial contrast agent will be calculated in months as follow: (first study contrast agent administration date - procedure date in days) / 30.4375.
This time and the imaging procedure will be tabulated by series and overall using FAS1 and FAS2.

Listing of trial disease diagnosis and imaging procedure will be presented in CSR Appendix 16.2.4

5.4.3. Medical history and concomitant diseases

Summary tables (number and % of patients) grouped by SOC and PT will be presented for Medical history firstly then for concomitant diseases by series and overall using FAS1, FAS2 and by contrast agent group using Safety set. Tables will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT according to the overall population.

Listing of medical history and concomitant diseases will be presented in CSR Appendix 16.2.4.

5.4.4. Clinical laboratory evaluation at baseline

eGFR data will be presented at V2 and V4 using the Safety set by contrast agent group. eGFR data will be analyzed quantitatively and qualitatively. Qualitative analyses will present number of patients with value <30 mL/min/1.73m^2, ≥30 and <60 mL/min/1.73m^2, ≥60 and <90 mL/min/1.73m^2, ≥90 mL/min/1.73m^2. Quantitative analyses will be done by tabulating raw data.
Listing of eGFR data will be presented in CSR Appendix 16.2.8.

5.4.5. Vital signs, physical findings and other observations related to safety at baseline

Physical examination not performed and reason will be listed in CSR Appendix 16.2.4. Vital signs will be only presented in the safety section.

5.4.6. Prior medications

Summary tables (number and % of patients) grouped by the first and the fourth level of Anatomical Therapeutic Chemical (ATC) code will be presented by series and overall for prior medication using FAS1 and FAS2. Tables will be sorted by descending frequency of ATC1 (anatomical class) and, within each ATC1, by descending frequency of ATC4 (chemical class) according to the overall column.
Listing of prior medications will be presented in CSR Appendix 16.2.4.

5.4.7. Other baseline characteristics

Frequency and percentages will be tabulated by contrast agent group and overall for patient intolerance history related to contrast agent using Safety set.
Listing of patient intolerance history related to contrast agent will be presented in CSR Appendix 16.2.4

5.5. MRI examination

MRI examination will be presented using the FAS1 and FAS2. Analysis using FAS1 will show only MRI examination when gadopiclenol is administered. Analysis using FAS2 will show MRI examination by contrast agent group.
MRI examination performed and magnetic field strength (1.5 or 3.0 tesla) will be tabulated by contrast agent group.

Listing of MRI examination data will be presented in CSR Appendix 16.2.5.

5.6. Efficacy evaluation

5.6.1. Primary analysis of the primary criteria

Superiority of Paired versus Pre-contrast images of gadopiclenol regarding lesion visualization co-primary criteria (primary criteria 1)

Each co-primary criterion will be analyzed on the FAS1 using a general linear model for each reader independently, modelling the patient's score as a function of the MRI modality ("Pre" MRI and "Paired" MRI) with adjustment on repeated measures on the patient due to the pairing of MRI modalities in patients.

Hence for each off-site reader, the models will be the following:

- Border delineation = MRI modalities + error
- Internal morphology = MRI modalities + error
- Degree of contrast enhancement = MRI modalities + error

The parameters of the general linear model will be estimated using the SAS® procedure Mixed. The procedure used for the superiority analysis will be the following for each co-primary criterion and each off-site reader:

```
proc mixed data = XXX method = REML;
  class subject MRI;
   model score = MRI;
   repeated MRI / subject=subject  type = cs;
/* To get the one-sided p-value of the paired t-test*/
   lsmeans MRI / pdiff = controlu('PRE') tdiff cl alpha = 0.025;
/* To get the estimate and the corresponding confidence interval of the paired difference */
   lsmeans MRI;
   estimate "PAIRED - PRE" MRI 1 -1 /cl;
run; .
```

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

In order that superiority of the "Paired" MRI over the "Pre" is statistically demonstrated, 2 out of 3 readers will have to meet the alternative hypothesis for the three co-primary criteria in the gadopiclenol group i.e., a statistically significant (one-sided p-value is equal or less than 0.025) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions.

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

In the framework of the co-primary criteria (EMA request), this analysis will be performed using the PPS2.
Each co-primary criterion will be analyzed using a general linear model for each reader independently, modelling the patient's score as a function of period and contrast agent (Gadolinium Based Contrast Agent (GBCA): gadopiclenol and gadobutrol) with repeated measures on the patient due to the pairing of contrast agents in patients.

Hence for each off-site reader, the models will be the following:

- Border delineation = contrast agent group + period + error
- Internal morphology = contrast agent group + period + error
- Degree of contrast enhancement = contrast agent group + period + error

The parameters of the general linear model will be estimated using the SAS® procedure Mixed. The procedure used for the non-inferiority analysis will be the following for each co-primary criterion and each off-site reader:

```
proc mixed data = XXX method = REML;
  class subject GBCA period;
   model score = GBCA period;
   repeated GBCA / subject=subject / type = cs;
/* To get the estimate and the corresponding confidence interval of the paired difference */
   lsmeans GBCA;
   estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
run;
```

The Student's t-based 95% CIs of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 co-primary criteria on matching lesions. Results will be presented per off-site reader.

If the lower bound of this CI is above the non-inferiority margin for at least 2 out of 3 readers and for the 3 co-primary criteria, then non-inferiority between gadopiclenol and gadobutrol will be concluded.

As soon as the non-inferiority is demonstrated, the superiority of the gadopiclenol over gadobutrol will be tested using the same method by comparing the lower bound to zero instead of the non-inferiority margin. No adjustment for multiplicity is needed as it is a simple closed testing procedure.
If the lower bound of the Student's t-based 95% CIs of the difference between gadopiclenol and gadobutrol is above 0 for at least 2 out of 3 readers and for the 3 co-primary criteria, then superiority of gadopiclenol over gadobutrol will be concluded.

5.6.2. Secondary analysis

Additional analyses of the primary analyses

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

Supportive analyses of the superiority analysis
The superiority analysis will be repeated using the PPS1.

Descriptive statistics
The 3 co-primary criteria will be summarized by contrast agent groups and MRI modalities (pre and paired) using the FAS1, FAS2, PPS1 and PPS2. Analyses using FAS1 and PPS1 will show only co-primary criteria when gadopiclenol is administered.

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

Examinations of subgroups

Descriptive statistics:
The 3 co-primary criteria will be summarized by contrast agent groups, MRI modalities (pre & paired) and each of main demographic parameter (categorized age, sex, race, ethnicity, geographic region) and magnetic field using FAS1 and FAS2. Analysis using FAS1 will show only co-primary criteria when gadopiclenol is administered.

Model:
In addition to the primary analyses, sensitivity analyses of the superiority analysis (on the FAS1) and of the non-inferiority analysis (on the FAS2) will be conducted using the same linear model with each of main demographic parameters and magnetic field as additional factors. Each demographic parameter and magnetic field will be analyzed independently using the model of the primary analyses.

The model syntax will be as follows for the sensitivity analysis of the superiority:
proc mixed data = XXX method = REML;
class subject MRI subgroup;
model score = MRI subgroup MRI*subgroup;
repeated MRI / subject=subject / type = cs;
lsmeans MRI subgroup MRI* subgroup / pdiff = controlu('PRE') tdiff cl alpha = 0.025;
estimate "PAIRED - PRE" MRI* subgroup 1 -1 …../cl;
run; .

The model syntax will be as follows for the sensitivity analysis of the non inferiority:
proc mixed data = XXX method = REML;
class subject GBCA subgroup period;
model score = GBCA subgroup period GBCA*subgroup;
repeated GBCA / subject=subject / type = cs;
lsmeans GBCA subgroup GBCA*subgroup / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
estimate "gadopiclenol – "gadobutrol" GBCA*subgroup 1 -1 …./cl;
run; .

Results of the model (difference of the least square means) will be tabulated and presented graphically by means of forest plot.

Intra-reader variability
Intra-reader variability will be analyzed in a subgroup of 10% of patients randomly selected for whom the off-site readers have re-read the images.
Intra-reader variability will be presented using data from gadopiclenol period on FAS1 on the one hand and using paired images from gadopiclenol and gadobutrol on FAS2 on the other hand.
Intra-reader variability will be studied by a Bland-Altman graph:

- Average of 1st and 2nd reading on X axis.
- Difference 2nd reading - 1st reading on Y axis.
- Horizontal lines at 0, Mean + 1.96SD and Mean - 1.96SD, where Mean and SD are the mean and the SD of the averages of 1st and 2nd readings.

One scatter plot per reader will be presented.

Descriptive statistics and the Intra-Class Correlation (ICC) will also be provided. It will be based on a one-way random effect model without observed effect:

$$Y_{ijk} = \mu + \alpha_i + \varepsilon_{ijk}$$

with $\alpha_i \sim N(0,\sigma_\alpha^2)$ and $\varepsilon_{ijk} \sim N(0,\sigma_\varepsilon^2)$ and ε_{ijk} is independent of α_i.

$$ICC = \sigma_\alpha^2 / (\sigma_\alpha^2 + \sigma_\varepsilon^2)$$

which is estimated by

$$(MS_\alpha - MS_\varepsilon) / (MS_\alpha + MS_\varepsilon)$$

where MS_α and MS_ε are the mean sums of squares from the one-way ANalysis Of VAriance (ANOVA) model for between and within subjects, respectively.

SAS® procedure used for the analyses of this secondary efficacy criterion will be the following for each off-site reader:

```
ods output OverallANOVA =icc0;
proc glm data=intra;
  class subject reading;
  model score = subject reading;
run;
data ICC;
  retain sb sw;
  set icc0 end=last;
  if source='Model' then sb=ms;
  if source='Error' then sw=ms;
  if last then do;
    ICC=round((sb-sw)/(sb+sw), 0.01);
    output;
  end;
run;
```

Inter-reader variability

Inter-reader variability will be evaluated using the first reading only, since each case was read by 3 different readers and allow comparisons between readers.

Inter-reader variability will be presented using data from gadopiclenol period on FAS1 on the one hand and using paired images from gadopiclenol and gadobutrol on FAS2 on the other hand.

The same methodology as the one presented above for intra-off-site variability will be applied. One scatter plot (Bland & Altman graph) for each of the 3 comparisons will be presented. The factor “reader” will be used instead of the factor “reading” in the model.

Presentation of patients and lesions.

Number of patients and lesions by contrast agent and MRI modalities for all efficacy datasets will be displayed using All Randomized Set.

Global model

The primary analysis 2 will be repeated with only one model putting all off-site readers together and so including the reader as covariate using the FAS2. The results will be presented overall.

Non-matching lesions

The primary analyses 1 and 2 will be repeated including the non-matching lesions as well using the extended FAS1 and extended FAS2 respectively.

Dropout patients
If the number of patients dropping out is different between series, then the primary analysis 2 will be repeated using All Randomized Set considering in the model as well, the patients having discontinued between period 1 and period 2. As the discontinued patients do not have matching lesion by definition, the analysis will take into account all lesions including the not matching ones.

Check of normality assessment
Normal Probability Plot where the ranked residual values are plotted against the normal scores will be displayed for the two primary analyses (any reader and any assessment - *pre and paired* - confounded).

Analysis of secondary criteria

All analyses of the secondary criteria will be done using the extended FAS1 and extended FAS2 except otherwise specified. Tables using extended FAS1 will include only data from the MRI using gadopiclenol.

Lesion visualization (on site read, i.e., performed by the investigator)
The same analyses as lesion visualization co-primary criteria (off-site) will be performed except intra and inter reader variability assessment and except examinations of subgroups.

Improvement in patient-level lesion visualization scores, paired versus pre-contrast images
Improvement in patient-level lesion visualization will be calculated for the 3 co-primary criteria by reader and will be tabulated by contrast agent groups; off-site and on-site reader's outcomes will be separately presented using FAS 1 and FAS 2 for off-site outcomes and extended FAS 1 and extended FAS 2 for on-site outcomes..

Lesion visualization at lesion level (off site read)
Each lesion visualization criterion will be analyzed by reader using a general linear model, modelling the lesion score as a function of the center, period and on the one hand, contrast agent group (GBCA: gadopiclenol and gadobutrol) with repeated measures on the lesion due to the pairing of contrast agents in lesions and on the other hand, modality of the MRI (pre and paired images) with repeated measures on the lesion due to the pairing of MRI modalities in lesions. Matching and no matching lesions will be kept in the analysis.

Hence the models will be the following for gadobutrol vs. gadopiclenol:
- Border delineation = contrast agent group + period + center + error
- Internal morphology = contrast agent group + period + center + error
- Degree of contrast enhancement = contrast agent group + period + center + error

and the following for pre vs. paired within gadopiclenol MRI period:
- Border delineation = MRI modality + period + center + error
- Internal morphology = MRI modality + period + center + error
- Degree of contrast enhancement = MRI modality + period + center + error

The parameters of the general linear model will be estimated using the SAS® procedure Mixed. The procedure used for the analysis will be the following for each criterion:

```
proc mixed data = XXX method = REML;
  class lesion_# GBCA (or MRI modality) period reader center;
   model score = GBCA (or MRI modality) period reader center;
   repeated GBCA / subject=lesion_#/ type = cs;
/* To get the estimate and the corresponding confidence interval of the paired difference */
   lsmeans GBCA (or MRI modality);
```

estimate "gadopiclenol - gadobutrol" GBCA (or "Paired – Pre" MRI modality) 1 -1 /cl;
run;

The Student's t-based 95% CIs of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 lesion visualization criteria. The Student's t-based 95% confidence intervals of the difference between paired and pre will be constructed for each of 3 lesion visualization criteria.

Technical adequacy of images
The quality of images will be assessed by off-site readers and on-site radiologists. Technical adequacy and assessable status of images will be tabulated by contrast agent groups and MRI modalities (pre and paired) using All Randomized Set; off-site and on-site reader's outcomes will be separately analyzed. Non assessable reasons will be only listed.

Number of lesions
The number of lesions by patient will be assessed by off-site readers and on-site radiologists and will be tabulated (as quantitative parameter and in class: No lesion / 1 lesion / 2 lesions / 3 lesions / More than 3 lesions) by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.

The number of lesions will be fitted by a multivariate model using the negative binomial distribution. The model will include the factors period contrast agent group and MRI modalities (pre and paired). Each off-site reader will be analyzed by a specific model and on-site reading will be analyzed in the same way. The parameters of the model will be estimated using the SAS® procedure Glimmix. The difference between contrast agent groups using extended FAS2 and between MRI modality using extended FAS1 in mean of lesions detected and associated 95% CI will be computed.

Procedure used will be the following for each off-site reader and on-site reading:
for the difference between contrast agent groups
proc glimmix data = XXX;
class subject GBCA period;
model nblesions = GBCA period / dist = negbin link = id;
random _residual_ / subject = subject;
lsmeans GBCA / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
lsmeans GBCA;
estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
run;

for the difference between MRI modalities (limited on gadopiclenol period)
proc glimmix data = XXX;
class subject MRI;
model nblesions = MRI modality / dist = negbin link = id;
random _residual_ / subject = subject;
lsmeans MRI/ pdiff = controlu('PRE') tdiff cl alpha = 0.025;
lsmeans MRI;
estimate "Paired - Pre" MRI 1 -1 /cl;
run;

Size of lesions
The size (largest diameter) of the 3 most representative lesions by patient will be measured by off-site readers and on-site radiologists and will be summarized by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.

Location
The location of the 3 most representative lesions by patient will be assessed by off-site readers and on-site radiologists and will be displayed by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.

Diagnostic confidence
The diagnosis for the patient and level of diagnostic confidence according to off-site readers and on-site radiologists will be displayed by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.
Level of diagnostic confidence will be summarized qualitatively and quantitatively by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.

Impact of contrast-enhanced MRI on patient treatment plan
The impact on patient treatment plan will be tabulated by contrast agent groups. The therapeutic management proposed based on combined unenhanced and contrast-enhanced MRI vs the one based on unenhanced MRI will be tabulated for all patients having the treatment plan be changed.

The impact on patient treatment plan will be tabulated by contrast agent groups and tumor classification before GBCA administration using extended FAS2.

The tumor classification is based on diagnosis done at unenhanced MRI according to the following:

Diagnosis	Tumor classification
Glial tumor, low grade (I/II)	Non Malignant
Glial tumor, high grade (III/IV)	Malignant
Glial tumor, tumor grade cannot be determined	Not assessable
Meningioma	Non Malignant
Schwannoma	Non Malignant
Pituitary adenomas	Non Malignant
Brain metastasis	Malignant
Spine metastasis	Malignant
Inflammatory disease	
Abscess	
Stroke	
Vascular malformation	
Other	
Not assessable	Not Assessable

All diagnosis will not be classified and so not presented in the analysis.

The impact on patient treatment plan will be fitted by a multiple logistic regression model for correlated data. The model will include the factors contrast agent group and tumor classification before administration (malignant / not malignant / not assessable). The parameters of the model will be estimated using the SAS® procedure glimmix. The difference between contrast agent groups in proportions and associated 95% CI will be computed globally and for each tumor classification.

```
proc glimmix data = XXX;
  class subject GBCA tumor_cl;
  model eval = GBCA tumor_cl GBCA*tumor_cl / dist = bin link =I  ddfm = kr;
  random _residual_ / subject = patient type = cs;
  estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
  estimate "gadopiclenol – gadobutrol for malignant tumor" GBCA*tumor_cl 1 0 -1 0 /cl;
```

```
  estimate "gadopiclenol – gadobutrol for non malignant tumor" GBCA*tumor_cl 0 1 0 -1 /cl;
  estimate "gadopiclenol – gadobutrol for not assessable tumor" GBCA*tumor_cl 0 1 0 -1 /cl;
run;
```

Contrast to Noise Ratio (CNR)

CNR is calculated from the Signal Intensity (SI) measurement of maximum 3 most representative lesions by the 3 independent off-site readers. The mean of CNR will be calculated by patient and by MRI modality using only matching lesions between GBCA. Once the matching lesions between GBCA have been determined, only these ones will be kept for the CNR calculation of pre-contrast.

For each reader, CNR will be tabulated by contrast agent groups on pre contrast and Paired images using FAS2.

Differences between contrast agents will be tested using a paired Student's t-test. The models will include the contrast agent group, the period and the unenhanced value (Pre) as covariate. The parameters of the general linear models will be estimated using the SAS® procedure Mixed. The difference between contrast agent groups in mean score and associated 95% two-sided CI will be computed.

Procedure used will be the following for each off-site reader:

```
Proc mixed data = XXX method = REML;
  class subject trt period;
   model score = GBCA period pre;
   repeated GBCA/subject= subject / type = cs;
   lsmeans GBCA / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
/* The following code is needed as previous statement lsmeans does not provide the upper limit of CI */
   lsmeans GBCA;
   estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
run; .
```

Percentage Enhancement of lesions (E%)

E% is calculated from the SI measurement of maximum 3 most representative lesions by the 3 independent off-site readers. The mean of E% will be calculated by patient using only matching lesions between GBCA.

For each reader, E% will be tabulated by contrast agent groups using FAS2. Differences between contrast agents will be tested using a Student's t-test. The models will include the contrast agent group and the period. The parameters of the general linear models with repeated measures will be estimated using the SAS® procedure Mixed. The difference between contrast agent groups in mean score and associated 95% two-sided CI will be computed.

The SAS® procedure used for the analysis will be the following:

```
proc mixed data = XXX method = REML;
  class subject GBCA period;
   model score = GBCA period;
   repeated GBCA/subject= subject / type = cs;
   lsmeans GBCA / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
/* The following code is needed as previous statement lsmeans does not provide the upper limit of CI */
   lsmeans GBCA;
   estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
run; .
```

Lesion to Background Ratio (LBR)

LBR is calculated from the SI measurement of maximum 3 largest representative lesions by the 3 independent off-site readers. Then, the mean LBR will be calculated by patient and by MRI modality including matching lesions only.

Once the matching lesions between GBCA have been determined, only these ones will be kept for the LBR calculation of pre-contrast.
For each reader, LBR will be tabulated by contrast agent groups on pre contrast and post images evaluated on paired using FAS2. Differences between contrast agents will be tested using a Student's t-test. The models will include the contrast agent group, the period and the unenhanced value (pre) as covariate. The parameters of the mixed models will be estimated using the SAS® procedure Mixed. The difference between contrast agent groups in mean score and associated 95% two-sided CI will be computed.

Procedure used will be the following for each off-site reader:

```
Proc mixed data = XXX method = REML;
  class subject GBCA period;
   model score = GBCA period pre;
   repeated GBCA/subject= subject / type = cs;
   lsmeans GBCA / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
/* The following code is needed as previous statement lsmeans does not provide the upper limit of CI */
   lsmeans GBCA;
   estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
run; .
```

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

The SAS® procedure used for this analysis will be:

```
proc univariate data=XXX;
  class reader;
  var pref;
  output out=XXX probs=PROBS;
run;
```

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

Listing of efficacy data will be presented in CSR appendix 16.2.6.

5.7. Safety Evaluation

The safety evaluation will be presented using the Safety Set except otherwise specified.

5.7.1. Extent of Exposure

Time between inform consent signed and 1st IMP administration, 1st and 2nd IMP administrations, 2nd injection of contrast agent and patient's last contact and inform consent signed and patient's last contact in days, volume actually administered, actual injection rate, location of injection site, mode of injection, injection of saline flush and occurrence of an overdose will be tabulated. Frequency tabulation of actual injection rate according to following classes: <2 mL/s, between 2 and 3 mL/s including, >3mL/s will be also displayed per contrast agent group.
Weight measured at each trial product administration will be presented by contrast agent groups.
Listing of exposure will be presented in CSR appendix 16.2.5.

5.7.2. Adverse Events

AEs will be described systematically in terms of number and percentage of patients with AEs and in terms of number of AEs. AEs will be displayed by periods (MRI 1 and MRI 2) and overall.

AEs emergence will be defined as follows:

- Non-treatment emergent AE (NTEAE): if the AE starts prior to the 1st injection (pre-injection) or if the patient is not injected.
- Treatment emergent AE (TEAE): if the AE starts after the 1st injection (post-injection).
    - If it starts between the 1st injection and the 2nd injection (<), then it will be considered as a TEAE associated with the 1st contrast agent of the patient's series (MRI 1).
    - If it starts after the 2nd injection (≥), then it will be considered as a TEAE associated with the 2nd contrast agent of the patient's series (MRI 2).

Time to onset of AE will be calculated as follow: datetime of AE start – datetime of last start time of injection of IMP administration before AE

Overall Safety Summary

An overall summary of NTEAEs will be presented using the SPS. The table will be presented with the overall "Total" column only.

The total number of events and number of patients with at least one event will be tabulated for the following events:

- All AEs.
- Serious AEs (SAEs) (variable "serious" classified as yes or missing) and by Seriousness criteria (patients with AEs having different seriousness criteria will be counted in each category of seriousness criterion).
- AEs of special interest (AESIs) (preferred term is Nephrogenic systemic fibrosis).
- AEs with causal relationship to a trial procedure.
- AEs according to intensity (patients with AEs having different intensities will be counted in each category of intensity).
- AEs according to the outcome (patients with AEs having different outcomes will be counted in each category of outcome).
- AEs requiring a concomitant drug (AE-targeted medication).
- AEs requiring a concomitant procedure/therapeutic measures (other AE-targeted action).
- AEs leading to trial discontinuation.

Furthermore the distribution of the number of AEs reported by patient (0, 1, 2 or 3 or more AEs) will be also presented.

TEAEs

The same table will be displayed by contrast agent groups and periods for Treatment Emergent AEs (TEAEs). The terms "NTEAE" will be replaced by "TEAE". The following variables will be presented in addition:

- TEAEs with causal relationship to the IMP.
- TEAEs leading to interruption of the IMP.
- TEAE leading to IMP unblinding

The number and percentage of patients with at least one TEAE and the number of TEAE will be presented by contrast agent groups and period and overall (overall by contrast agent group and total overall) according to Primary SOC and PT.

The table will be sorted by descending frequency of SOC and, within each SOC by descending frequency of PT according to the overall column.

TEAEs with Causal Relationship to the IMP

The number and percentage of patients with at least one TEAE with causal relationship to the IMP and the number of corresponding TEAE will be presented by contrast agent groups and period and overall according

to Primary SOC and PT. AEs with causal relationship to the IMP are those described by the investigator with causal relationship to the IMP "related" or missing.

TEAEs with Causal Relationship to a Trial Procedure

The number and percentage of patients with at least one TEAE with causal relationship to a trial procedure and the number of corresponding TEAE will be presented by contrast agent groups and period and overall according to Primary SOC and PT. AEs with causal relationship to a trial procedure are those described by the investigator with causal relationship to a trial procedure "related" or missing.

Deaths, serious adverse events and other significant adverse events

Deaths, AESI and SAEs will be listed (if any). These listings will be sorted by patient number, date/time of onset, end date, Primary SOC, High Level Group Term (HLGT), High Level Term (HLT), PT, Lowest Level Term (LLT) and description.

Listing of adverse events will be presented in CSR appendix 16.2.7.

5.7.3. Clinical laboratory evaluation

All laboratory values recorded during the trial will be individually listed and flagged for values outside reference ranges if any (presented in CSR appendix 16.2.8). Parameters obtained centrally and those obtained locally will be presented together.

Hematology data include the following parameters (in SI and conventional units):

	SI units	Conventional units
Red Blood Cells (RBC) = Erythrocytes	10^{12} /L	10^{6} /µL
White Blood Cells (WBC) = Leukocytes	10^{9} /L	10^{3} /µL
Neutrophils	10^{9} /L	10^{3} /µL
Neutrophils/ Leukocytes	%	%
Eosinophils	10^{9} /L	10^{3} /µL
Eosinophils/ Leukocytes	%	%
Basophils	10^{9} /L	10^{3} /µL
Basophils/ Leukocytes	%	%
Lymphocytes	10^{9} /L	10^{3} /µL
Lymphocytes/ Leukocytes	%	%
Monocytes	10^{9} /L	10^{3} /µL
Monocytes/ Leukocytes	%	%
Platelet count	10^{9} /L	10^{3} /µL
Hemoglobin	g/L	g/dL
Hematocrit	v/v	%
Mean Corpuscular Volume (MCV)	fL	fL

Biochemistry data include the following parameters:

	SI units	Conventional units
Sodium	mmol/L	mEq/L
Potassium	mmol/L	mEq/L
Chloride	mmol/L	mEq/L
Blood Urea Nitrogen (BUN)	mmol/L	mg/dL
Urea*	mmol/L	mg/dL
Serum creatinine	umol/L	mg/dL
eGFR	mL/min/1.73m²	mL/min/1.73m²

	SI units	Conventional units
Total protein	g/L	g/dL
Calcium	mmol/L	mg/dL
Phosphorus	mmol/L	mg/dL
Total bilirubin	umol/L	mg/dL
Indirect bilirubin	umol/L	mg/dL
Conjugated bilirubin	umol/L	mg/dL
Aspartate Amino Transferase (AST)	U/L	U/L
Alanine Amino Transferase (ALT)	U/L	U/L
Alkaline Phosphatase	U/L	U/L
Lactate DeHydrogenase (LDH)	U/L	U/L
Triglycerides	mmol/L	mg/dL
Cystatin C	mg/L	mg/L

*Urea is derived from BUN. In SI unit, Urea=BUN, in conventional unit, Urea=BUN*2.14

The baseline value for each laboratory parameter will be the last value measured before the first contrast agent administration (i.e. the assessment prior to 1st MRI).

Quantitative analysis
Descriptive statistics of raw data and change from baseline for hematology and biochemistry parameters at visits 2, 3, 4 and 5 will be described as quantitative variables in both SI and conventional units. Numbers and percentages of patients with values out of range (lower than the lower limit or higher than the upper limit of normal range) will also be presented, except if values for normal ranges are unknown for a parameter.

Qualitative analysis
Shift tables presenting relative change from baseline in classes *versus* baseline in classes will be displayed for *serum creatinine, eGFR, BUN* and *cystatin C*.
Baseline data will be classified as follows (no baseline categories will be used for cystatin C):

SI units	Conventional units
• Serum creatinine (umol/L): o < 60 o ≥ 60 and < 100 o ≥ 100	• Serum creatinine (mg/dL): o < 0.66 o ≥ 0.66 and < 1.1 o ≥ 1.1
• eGFR (mL/min/1.73m²): o < 60 o ≥ 60 and < 90 o ≥ 90	• eGFR (mL/min/1.73m²): o < 60 o ≥ 60 and < 90 o ≥ 90
• BUN (mmol/L): o < 2 o ≥ 2 and < 4 o ≥ 4 and < 6 o ≥ 6	• BUN (mg/dL): o < 5.6 o ≥ 5.6 and < 11.2 o ≥ 11.2 and < 16.8 o ≥ 16.8
• Cystacin C (mg/L): o All	• Cystacin C (mg/L): o All

Relative change from baseline will be calculated as follows: 100* (post injection measurement - baseline measurement) / baseline measurement. Relative change from baseline will be classified as follows:

- ≤ -50%.
- > -50% and ≤ -25%.
- > -25% and ≤ -15%.
- > -15% and < 0%.
- ≥ 0% and < 15%.
- ≥ 15% and < 25%.
- ≥ 25% and < 50%.
- ≥ 50%.

Numbers and percentages of patients in each class will be presented in both SI and conventional units.

In the tables and listings, the parameters will be ordered as follow:

• Hematology: RBCs, hemoglobin, hematocrit, MCV, WBCs=leukocytes, neutrophils, neutrophils/leukocytes, lymphocytes, lymphocytes /leukocytes, monocytes, monocytes/leukocytes, eosinophils, eosinophils/leukocytes, basophils, basophils/leukocytes and platelet count.

• Biochemistry: sodium, potassium, chloride, calcium, phosphorus, total protein, serum creatinine, eGFR, BUN, Urea, Cystatin C, AST, ALT, alkaline phosphatase, total bilirubin (and indirect bilirubin), conjugated bilirubin, Triglycerides, LDH.

Individual clinically significant abnormalities

Hematology and biochemistry parameter of patients with at least one clinically significant value (according to the investigator) during the trial will be listed.

5.7.4. Vital signs, physical findings and other observations related to safety

Raw values and changes from baseline of Systolic/Diastolic Blood Pressure (mmHg) and Pulse Rate (beats/min) will be summarized by period, timepoint and contrast agent group.

Descriptive statistics of raw data and change from baseline for each vital signs' parameter will be computed at each time point. The baseline value will be the last vital signs measured prior to the injection of the 1st contrast agent.

Vitals signs of patients with at least one clinically significant value (according to the investigator) during the trial will be listed.

Injection-site tolerance will be summarized qualitatively by timepoint and contrast agent group. Pain evaluation will be additionally quantitatively summarized by timepoint and contrast agent group.

Listings of injection-site tolerance and vital signs will be provided in CSR appendix 16.2.9.

5.7.5. Concomitant medications/procedures

The number and percent of patients taking concomitant medications and concomitant procedures will be presented by contrast agent group and overall. According to the information available in the clinical database, a medication/procedure can be concomitant to the two periods (if any) and so counted in both contrast agent groups. In this case, it will count only once in the total column.

Summary tables (number and % of patients) grouped by the first and the fourth level of ATC code will be presented for concomitant medications. Tables will be sorted by descending frequency of ATC code 1 (anatomical class) and, within each first ATC, by descending frequency of ATC code 4 (chemical class) according to the column Total.

Summary tables (number and % of patients) grouped by SOC and PT will be presented for concomitant procedures and will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of the PT according to the column Total.

Listing of all medications/procedures will be presented in CSR appendix 16.2.4.

6. LIST OF TABLES, FIGURES AND LISTINGS

6.1. Contents of clinical study report section 14

This section lists all Tables and Figures in the order in which they are expected to appear in Section 14 of the CSR.

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Table 14.1.3.1 Analysis Data Sets: Full Analysis and Per Protocol Sets– Screened patients Set
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Table 14.1.4.8 Medical History According to Primary SOC and PT - FAS1
Table 14.1.4.9 Concomitant Disease According to Primary SOC and PT - FAS1
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Table 14.1.4.12 Medical History According to Primary SOC and PT - Safety Set
Table 14.1.4.13 Concomitant Disease According to Primary SOC and PT - Safety Set
Table 14.1.4.14 eGFR at Visit 2 and Visit 4 - Safety Set
Table 14.1.4.15 Prior Medications according to ATC first and fourth levels - FAS1
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Table 14.1.4.17 Patient's Contrast Agent Intolerance History - Safety Set

6.1.1.5 MRI Examination
Table 14.1.5.1 MRI Examination - FAS1
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6.1.1.6 Compliance with Trial product
Table 14.1.6.1 Compliance with Trial product – FAS1
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6.1.2. Efficacy data

6.1.2.1 Primary Efficacy Co-primary Criteria

Primary Analysis of the Co-primary Criteria

Table 14.2.1.1 Co-primary criteria 1 - Off-Site Readings – Mixed Model – FAS1
Table 14.2.1.2 Co-primary criteria 2 - Off-Site Readings – Mixed Model – PPS2

Supportive Analyses of the Co-primary criteria

Table 14.2.1.3 Co-primary criteria 1 - Off-Site Readings – Mixed Model – PPS1
Table 14.2.1.4 Co-primary criteria 2 - Off-Site Readings – Mixed Model – FAS2

Descriptive Statistics

Table 14.2.1.5 Co-primary criteria 1- Off-Site Readings - Descriptive Statistics - FAS1
Table 14.2.1.6 Co-primary criteria 1- Off-Site Readings - Descriptive Statistics - PPS2
Table 14.2.1.7 Co-primary criteria 2- Off-Site Readings - Descriptive Statistics – PPS1
Table 14.2.1.8 Co-primary criteria 2- Off-Site Readings - Descriptive Statistics – FAS2

Assay sensitivity

Table 14.2.1.9 Lesion visualization criteria - Off-Site Readings – MRI with Gadubutrol– PAIRED vs PRE - Mixed Model - FAS2

Additional Analyses of the Primary Criterion

Intra- Off-Site Reader Variability

Table 14.2.1.10 Lesion visualization criteria - Intra-Off-Site Reader Variability - FAS1
Figure 14.2.1.1 Lesion visualization criteria - Intra-Off-Site Reader Variability - Bland-Altman Graphs - FAS1
Table 14.2.1.11 Lesion visualization criteria - Intra-Off-Site Reader Variability – FAS2
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Inter- Off-Site Reader Variability

Table 14.2.1.12 Lesion visualization criteria - Inter-Off-Site Reader Variability - FAS1
Figure 14.2.1.3 Lesion visualization criteria - Inter-Off-Site Reader Variability - Bland-Altman Graphs - FAS1
Table 14.2.1.13 Lesion visualization criteria - Inter-Off-Site Reader Variability – FAS2
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Table 14.2.1.14 Lesion visualization criteria by demographic parameters and magnetic field - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE – Mixed Model – FAS1
Figure 14.2.1.5 Lesion visualization criteria - Off-Site Readings – Forest Plot by demographic parameters and magnetic field – FAS1
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Figure 14.2.1.6 Lesion visualization criteria - Off-Site Readings – Forest Plot by demographic parameters and magnetic field – FAS2

Table 14.2.1.16 Lesion visualization criteria by demographic parameters and magnetic field - Off-Site Readings - MRI with Gadopiclenol – Descriptive Statistics – FAS1

Table 14.2.1.17 Lesion visualization criteria by demographic parameters and magnetic field - Off-Site Readings - MRI with Gadopiclenol and MRI with Gadobutrol Descriptive Statistics – FAS2

Global analysis

Table 14.2.1.18 Co-primary criteria 2 - Off-Site Readings – Global Mixed Model with readers as covariate – FAS2

Presentation of number of patients and number of lesions

Table 14.2.1.19 Lesion visualization criteria - Off-Site Readings – Number of patients and lesions by contrast agent and by MRI modality (pre and paired) for all efficacy datasets - All Randomized Set

Non-matching lesions

Table 14.2.1.20 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE – Mixed Model including matching and non-matching lesions – Extended FAS 1

Table 14.2.1.21 Lesion visualization criteria - Off-Site Readings - MRI with Gadopiclenol– PAIRED vs PRE – Descriptive Statistics including matching and non-matching lesions - Extended FAS 1

Table 14.2.1.22 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model including matching and non-matching lesions – Extended FAS 2

Table 14.2.1.23 Lesion visualization criteria -Off-Site Readings – MRI with Gadopiclenol and MRI with Gadobutrol - Descriptive Statistics including matching and non-matching lesions - Extended FAS 2

Drop-out patients

Table 14.2.1.24 Lesion visualization criteria -Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Mixed Model including drop-out patients – All randomized Set

Table 14.2.1.25 Lesion visualization criteria - Off-Site Readings –MRI with Gadopiclenol and MRI with Gadobutrol Descriptive Statistics including drop-out patients - All Randomized Set

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Lesion visualization at lesion level (off site evaluations)

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Number of Lesions (on site and off site evaluations)

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7. REFERENCES

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8. APPENDICES