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STATISTICAL ANALYSIS PLAN

Efficacy and safety of gadoPiclenol foR bOdy MagnetIc reSonancE imaging (MRI)
Phase III Clinical Trial
The PROMISE trial

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BIOSTATISTICIAN [redacted]	**Date and Visa** [redacted]
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HISTORY FORM

Version	Date	Reason for change
V1.0	10 July 2019	Initial version
V2.0	25 January 2021	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 main demographic parameters and magnetic field 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 and addition of deviations Deviations: handling of potential deviation due to COVID pandemic Datasets analyzed: Addition of 3 datasets for efficacy analysis and precision of the presentation Demographics: in procedure for study diagnosis, addition of 3 classes (mammogram, Ultrasound, PET-CT) and indication of the selection by scanning the specify text when other is ticked Efficacy: secondary analysis of the primary criteria: addition of magnetic field in subgroup analysis and modification of the subgroup analysis by organ. 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 addition of analysis with non-matching lesions Efficacy: secondary analysis of the primary criteria: Lesion-level analysis with size of lesion added as co-factor. Efficacy: secondary criterion: patient's treatment plan: addition of analysis taken into account the nature (non malignant/malignant/not assessable) of the diagnosis done at unenhanced MRI Efficacy: secondary criterion: patient's treatment plan: addition of the therapeutic management based on unenhanced MRI Efficacy: secondary analysis of the primary criteria: Readers of different body regions put together in a way to have more balanced meta-readers in terms of concordance reads Exposure: addition of two periods for description, from inform consent signed to 1st IMP injection and from inform 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
eCRF	(electronical) Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
E%	Percentage enhancement of lesion
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
ICH	International Conference on Harmonization
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
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
SOC	System Organ Class
SPS	Screened Patient Set
TEAE	Treatment Emergent Adverse Event
WBCs	White Blood Cells
WHO-DD	World Harmonization Organization Dictionary Drug

TABLE OF CONTENTS

1. SUMMARY OF THE TRIAL PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, Protocol No. GDX-44-011 "Efficacy and Safety of Gadopiclenol for Body Magnetic Resonance Imaging (MRI) Phase III Clinical Trial".

This analysis plan is based on the Protocol Version N° 3.0 dated June 30, 2020 and the amendment for FRANCE dated June 30, 2020.

1.1. Trial objectives

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

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 patients referred for MRI of body regions, 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 patients referred for MRI of body regions.

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) for patients referred for MRI of the body regions (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
  - ✓ Subgroup analysis by organ and body region of the 3 lesion visualization co-primary criteria
  - ✓ 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
  - ✓ Percentage enhancement (E%) of lesion(s)

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

- o 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.

As different body regions are included in the study, readers with different expertise were needed for the reading of study images. Hence, according to the different anatomic locations, a pool of 18 readers are selected and qualified for the entire study images reads:

- 6 readers for Head and Neck (H&N): 3 readers for global pairs assessments, 3 readers for all other assessments
- 6 readers Thorax (including breast), Abdomen (including liver, pancreas and kidney), Pelvis (including uterus, ovary and prostate) put together and labelled as Body
- 6 readers Musculoskeletals (including extremities) (MSK)

Within each of the 3 groups, 3 reader are allocated s for global pairs assessments, 3 other readers for all other assessments (such as lesion visualisation parameters). Each group of readers will only read images as labelled by specific anatomic locations (H&N, Body and MSK).

As statistical analysis will be performed on the whole set of patients, 1 reader from each expertise domain are put together (1 reader H&N +1 reader Body + 1 reader MSK), 3 times. So, each reader presented in the report is a combination of 3 readers.
For almost all analyses including the 2 primary analyses, readers are put together based on the numbering (reader 1, reader 2 and reader 3) allocated by the imaging CRO in charge of the reading at the beginning of the trial before the start of the reading.

	Body	MSK	H&N
Reader 1= B1+MSK1+ H&N1	reader B1	reader MSK1	reader H&N1
Reader 2= B2+MSK2+ H&N2	reader B2	reader MSK2	reader N&H2
Reader 3= B3+MSK3+ H&N3	reader B3	reader MSK3	reader H&N3

In addition, Sensitivity analyses of the primary analyses using another affectation of readers from each expertise domain in each reader will be performed. The aim is to have a more homogeneous panel of readers, these sensitivity analyses will be run using grouping together the readers leading to have the 3 readers with the most homogeneous number of patients with matching lesions. Therefore, for the analyses pre vs paired in the gadopiclenol arm on one hand and for the analyses gadopiclenol vs. gadobutrol on paired images on the other hand, readers will be built by selecting the combination of readers from each expertise

domain for which the differences of the sum of each reader compared with the sum of the average across readers is minimal (see table below for an example).

	Body	MSK	H&N	
Reader 1	Radiologist B1	Radiologist MSK1	Radiologist HN1	Sum Reader1
Reader 2	Radiologist B2	Radiologist MSK2	Radiologist NH2	Sum Reader2
Reader 3	Radiologist B3	Radiologist MSK3	Radiologist HN3	Sum Reader3
	Average Body	Average MSK	Average H&N	Sum average

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).

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: Asia Pacific
- Hungary, France, Spain, Italy, Poland, Ukraine, Germany, Bulgaria: European countries

Other baseline characteristics are

- Imaging procedure documenting the trial disease
- Trial disease
- Medical history and concomitant diseases
- Patient' intolerance history related to contrast agent
- Prior medications defined as medications ended before the first administration.

Medical history and concomitant diseases will be coded in SOC and PT using the MedDRA latest version available at the date of data base lock. 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 WHODRUG dictionary latest version available at the date of data base lock.

MRI examination parameters are:

- MRI machine manufacturer name
- MRI machine field strength in tesla (1.5 or 3.0)
- Imaged body regions: Head and Neck, Thorax, Abdomen, Pelvis and Musculoskeletals

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 Reader (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 will be a qualitative assessment (not based on signal intensity measurement) according to the following scale:

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

The mean score for each of the 3 co-primary criteria of lesion visualization 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 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 as per meta-readers (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. Readers of this analysis will be meta-readers as described in the trial design section.
  Definitions of each co-primary criterion are provided in primary criteria 1 description.

- 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 on-site lesion visualization 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.

- 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 and for the 3 co-primary criteria, the mean score is calculated and compared between Pre contrast and Paired images. If the mean score in Paired images is greater than in Pre contrast images then the Paired image will be classified as "Better". If the mean score in Paired images is equal or less than in 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 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 size (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 eCRF his/her diagnosis (Malignant lesion, yes, no or 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 whether the patient treatment plan has changed based on the images obtained (yes/no). If yes, the therapeutic management proposed based on radiological assessment is the following:
  - Surgery
  - Biopsy
  - Chemotherapy
  - Radiotherapy
  - Other treatment: specify

The 2 quantitative criteria (E% and LBR) will be calculated in averaging the parameter for maximum 3 most representative lesions for each contrast agent (off-site read).

- 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)

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

where SI_{lesion} = Signal intensity of lesion
SI_b = Signal intensity of background (surrounding healthy tissue of the lesion)

- 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: when examination 1 is preferred to examination 2
  - 0: when no preference is observed
  - 2: 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 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 eGFR will be collected according to the following schedules:

- prior to each contrast agent injection (baseline value is from samples collected prior to the first contrast agent injection)
- one day after each contrast agent 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 from samples collected prior to the first agent injection)
- one day after each contrast agent 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 MedDRA dictionary last version at the time of the database lock.

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 dropped-out because of results of diagnostic of first period but rather for safety 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 [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. 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 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 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% 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 software used for the sample size assessment is 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. During the course of the study, the rate of non-valid primary criteria 1 was assessed and was eventually greater than expected (from 20% to 33%) leading to an increase of the sample size from 250 to 300 to maintain statistical power.

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% confidence interval (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 anomalies / lesions of various body organs is planned.

Therefore, a total number of 250 patients will allow a sufficient power to meet both objectives. During the course of the study, the rate of non-valid primary criteria 1 and 2 was assessed and was eventually greater

than expected (from 20% to 33%) leading to an increase of the sample size from 250 to 300 to maintain statistical power.

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. Mixed models will be performed only on patients with both MRIs for primary analyses.

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 procedure is collected, if the procedure is undergone the same day of the contrast media administration then the procedure will be affected to the contrast media administered this 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 is deemed enough. 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 organ, body region, 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 body regions, organs, demographic parameters and MRI machine field as additional factors.

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

Protocol was amended during the course of the trial to increase the sample size from 250 to 300 patients (amendment 2).
Indeed, 200 evaluable patients (defined as patients who completed the trial and with a valid primary criterion) are to be secured to allow a sufficient statistical power to meet both study primary objectives. The initial sample size calculation was based on a non-evaluable patient rate (drop-out rate and non-valid primary criterion rate) of 20% (50 patients), leading to a target of 250 enrolled patients.
Based on 245 patients currently enrolled (98% of planned target), 25 patients are already dropped-out. This drop-out rate is partially due to the Covid-19 pandemic preventing 6 patients from completing the trial up to now. Furthermore, Covid-19 pandemic may continue to impact enrollment of patients and/or protocol compliance.
In addition, the current estimated number of patients with no valid primary criterion is about 68 patients.
Altogether, this current estimation of 93 (25+68) non-evaluable patients is expected to increase before the recruitment completion. As a consequence, the revised hypothesis for the non-evaluable patient rate is now about 33%.

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

Five supplemental secondary analysis of lesion visualization criteria will be conducted in addition of those described in the final Protocol Version N° 3.0 (including amendment 2) dated June 30, 2020 and the amendment for FRANCE dated June 30, 2020:

- An analysis will be performed globally. Mixed model will be considered with patient and reader as adjustment factors.
- An analysis will be performed including non-matching lesions. Mixed model will be considered by reader with patient as adjustment factor.
- Two analyses will be performed at lesion level.
    - Plain: Mixed model will be considered by reader with patient and site as adjustment factors.
    - Lesion size based: Mixed model will be considered by reader with size of lesion, patient and site as adjustment factors.
- Additional subgroup analyses 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.

Further, the subgroup analysis by organ will include only following organs (Breast, Liver, Kidney, Pancreas, Prostate and those with more than 10% of patients for at least one reader). Patients with lesions in more than one organ will not be kept in the analysis.
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.

Analysis of secondary criterion: patient's treatment plan will be augmented by presenting the results according to the nature (non malignant/malignant/not assessable) of the diagnosis done at unenhanced MRI and by adding therapeutic management based on unenhanced MRI

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of patients

Number of patients attending each visit will be presented by series (gadopiclenol-gadobutrol / gadobutrol-gadopiclenol) and overall.
The patients' disposition 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. The same analyses will be repeated by body regions except reason of screen failure.
If a patient withdrew for Adverse Event and at least one adverse event 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 Adverse Event other than COVID-19
If a patient withdrew for other reason, then the reason of premature withdrawal will be derived from the specify field as the following:

Specifiy field	Reason of premature withdrawal
"COVID-19 crisis preventing patient to follow protocol schedule"	COVID-19 crisis 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 crisis
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: the Screened patients Set (SPS), the Safety Set (SS), the All Randomized Set (ARS), the Extended Full Analysis Set 1 & 2, the Full Analysis Set (FAS) 1 & 2 and the Per-Protocol Set (PPS) 1 & 2:

- 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 exam.
- 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 gadopiclenol pre contrast and paired images 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 both gadopiclenol and gadobutrol paired images 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	Safety Set	All Rando-mized Set	Extended Full Analysis Set		Full Analysis Set		Per Protocol Set	
			Extended FAS1	Extended FAS2	FAS1	FAS 2	PPS1	PPS2
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 contrast agent 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, IWRS).

If the reason of deviations is related to the COVID pandemic then it will be indicated 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: Patients with known	Clinical data base	**Major**

Category	Description	Source	Status
	or suspected lesion(s) referred for contrast-enhanced MRI of CNS or of heart or for MR Angiography.		
	Non inclusion criteria n°6 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
	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°6 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
	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** adequate	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 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 criteria2**
	Imaging protocol not respected with major impact on co-primary criteria for gadopiclenol administration	Monitoring	**Major**
	Imaging protocol not respected with major impact on co-primary criteria for gadobutrol administration	Monitoring	**Major criteria2**
	Imaging protocol not respected with non-major impact on primary criterion	Monitoring	Non major
	Deviation to blind charter in regards to data correction	Monitoring	Non major
Unblinding	Blind not maintained on site	Monitoring	Non major

Category	Description	Source	Status
	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 criteria2**
	Patient having received any MRI contrast agent from 3 days prior to first trial product administration, until 24 hours after the second trial product administration	Clinical data base	**Major**
	Patient having received any CT contrast agent from 3 days prior to first trial product administration, until 24 hours after the second trial product administration	Clinical data base	Non major
IMP deviation	Patient does not receive the IMP allocated by randomization	Clinical data base and IWRS data base	**Major**
	Patient does not receive the kit allocated by IWRS	Clinical data base and IWRS data base	Non 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 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 criteria2**
	Temperature excursion for IMP	Monitoring	Non major
	Temperature excursion for gadopiclenol with risk of freezing	Monitoring	**Major**
	Temperature excursion for gadobutrol with risk of freezing	Monitoring	**Major criteria2**
	IMP management not appropriate	Monitoring	Non major
	Extravasation during gadopiclenol administration	Clinical data base	**Major**
	Extravasation during gadobutrol administration	Clinical data base	**Major criteria2**
	Saline flush not done after IMP administration	Monitoring	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
	Ethnicity is missing	Clinical data base	Non major
	Race is missing	Clinical data base	Non major

Category	Description	Source	Status
	eGFR measurement at visit 3 or visit 5 is missing	Clinical data base	Non major
	Central Laboratory Biochemistry results **not** available	Laboratory data base	Non major
	Central Laboratory Hematology results **not** available	Laboratory data base	Non major
	Vital sign **result** 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 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 greater than 28 days	Clinical data base	**Major 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 criteria2**
	MRI machine used not qualified	Monitoring	Non major
	Body region is different between the two MRs	Clinical data base	Non major
	US patients with an indication other than Breast MRI	Clinical data base	Non major
	Physical examination **not** performed	Clinical data base	Non major
	eGFR method is not the same throughout the trial	Clinical data base	Non major
	eGFR method is not accurate	Clinical data base	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
	Tolerance at injection site 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
	Clinical protocol procedure not respected	Monitoring	Non major
GCP deviation	Deviations related to ICF signature process	Monitoring	Non major
	Source document management not appropriate	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 criteria1**" will be excluded from the PPS1
Patients presenting at least one protocol deviation with a status "**Major 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 SPS:

- 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 series and globally on the SPS 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 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.
The raw (mL) and relative (%) differences between theoretical and actual volumes of trial product will be tabulated.
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 sex, contraceptive status, 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. Same analyses will be repeated by body regions using FAS1 and FAS2 only.
Listing of demographics will be presented in CSR Appendix 16.2.4.

5.4.2. Trial disease

Trial disease diagnosis will be coded in System Organ Classes (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) latest version available at the date of data base lock. 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.

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.
For imaging procedure, in addition of the two existing pre-specified classes (MRI and CT) 3 classes (mammogram, Ultrasound, PET-CT) will be created. As they are not pre-specified, they will be classified by scanning the specify text when other is ticked according to the following algorithm:
If the upcased string of characters contains "ULTRASOUND" or "ULTRASONOGRAPHY" then the procedure will be classified as Ultrasound.
If the upcased string of characters contains "MAMMOGRAM" or "MAMMOGRAPHY" then the procedure will be classified as Mammogram.
If the upcased string of characters contains "PET-CT" or "PET/CT" or "PET CT" then the procedure will be classified as PET-CT.
Time and 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 for Medical history firstly then for concomitant diseases 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. Same analyses will be repeated by body regions using FAS1 and FAS2 only.

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. The ATC4 code will be added to the name in the table.
Listing of prior therapies 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 FAS 1 will show only MRI examination when gadopiclenol is administered. Analysis using FAS 2 will show MRI examination by contrast agent group.
MRI examination performed, magnetic field strength (1.5 or 3.0 tesla) and body regions will be tabulated by contrast agent group.
Listing of MRI examination and body regions 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 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 eval = 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 the FAS1 on matching lesions. Results will be presented per off-site reader.

In order that superiority of the "Paired" MRI over the "Pre" will be statistically demonstrated, 2 out of 3 readers will have to meet the alternative hypothesis for the three co-primary criteria in the gadopiclenol group: a statistically significant (one-sided p-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)

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 the contrast agent group (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 eval = 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% confidence intervals of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 co-primary criteria using the PPS2 on matching lesions. Results will be presented per off-site reader.

If the lower bound of this confidence interval 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. 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% confidence intervals 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 superiority analysis
The superiority analysis will be repeated using the PPS1.

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

Descriptive statistics
The 3 co-primary criteria will be summarized by contrast agent groups and MRI modalities (pre & 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

Body region
Descriptive statistics:
The 3 co-primary criteria will be summarized by contrast agent groups, MRI modalities (pre and paired) and body regions using FAS1 and FAS2. Analysis using FAS 1 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 body region as additional factors.

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

The robustness of MRI modality or GBCA effect across different body regions will be discussed with following information:

- Descriptive summary statistics for each body region
- Body region effect and body region *MRI modality/GBCA interactions tests. These tests are used as exploratory indexes meaning that conclusions of these tests are just used as a support for discussion. Absence of statistical significance should not be taken to imply consistency. Absence of statistical significance in an interaction test, or only directional consistency, would not be sufficiently sensitive filters to detect differences of potential interest.
- Effect estimations for each body region with the associated 95% two-sided CI. Overlapping of all body regions CI estimates with the confidence interval for the overall effect will be checked.
- Graphical visualization of the Body regions with a Forest plot for each body region of the LS Means difference and also the LS Means Ratio.

Organ
Patients having lesions in more than one organ will not be included in the analyses by organ. In addition, only the following organs (Breast, Liver, Kidney, Pancreas, Prostate and those with more than 10% of patients for at least one reader) will be kept in the analysis.

Descriptive statistics:
The 3 co-primary criteria will be summarized by contrast agent groups, MRI modalities (pre and paired) and organs using FAS1 and FAS2. Analysis using FAS 1 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 organ as additional factors.

The model syntax will be as follows for the sensitivity analysis of the superiority:

```
proc mixed data = XXX method = REML;
  class subject MRI organ;
  model eval = MRI organ MRI*organ;
   repeated MRI / subject=subject / type = cs;
   lsmeans MRI MRI* organ / pdiff = controlu('PRE') tdiff cl alpha = 0.025;
estimate "PAIRED - PRE" MRI* organ 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 organ period;
  model eval = GBCA organ period GBCA*organ;
   repeated GBCA / subject=subject / type = cs;
   lsmeans GBCA GBCA*organ / pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
estimate "gadopiclenol – "gadobutrol" GBCA*organ 1 -1 …./cl;
run; .
```

The robustness of MRI modality or GBCA effect across different organs will be discussed with following information:

- Descriptive summary statistics for each organ
- Organ effect and organ*MRI modality/GBCA interactions tests. These tests are used as exploratory indexes meaning that conclusions of these tests are just used as a support for discussion. Absence of statistical significance should not be taken to imply consistency. Absence of statistical significance in an interaction test, or only directional consistency, would not be sufficiently sensitive filters to detect differences of potential interest.
- MRI modality/GBCA effect estimations for each organ with the associated 95% two-sided CI. Overlapping of all organs CI estimates with the confidence interval for the overall effect will be checked by graphical visualization of the organs with a Forest plot for organ of the LS Means difference.

All these analyses will be performed for the co-primary criteria and statistical tests will be of help to "flag" potential problems, but descriptive assessments and clinical considerations need to be combined to evaluate potential signals.

Demographics parameters and magnetic field

Descriptive statistics:

The 3 co-primary criteria will be summarized by contrast agent groups, MRI modalities (pre and paired), each of main demographic parameter (categorized age, sex, race, ethnicity, geographic region) and magnetic field using FAS1 and FAS2. Analysis using FAS 1 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 models syntax will be as follows for the sensitivity analysis of the superiority:

proc mixed data = XXX method = REML;
class subject MRI demographic parameter (or magnetic field);
model eval = MRI demographic parameter (or magnetic field) MRI* demographic parameter (or magnetic field);
repeated MRI / subject=subject / type = cs;
lsmeans MRI demographic parameter (or magnetic field) MRI* demographic parameter (or magnetic field) / pdiff = controlu('PRE') tdiff cl alpha = 0.025;
estimate "PAIRED - PRE" MRI* demographic parameter (or magnetic field) 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 demographic parameter (or magnetic field) period;
model eval = GBCA demographic parameter (or magnetic field) period GBCA *body;
repeated GBCA / subject=subject / type = cs;
lsmeans GBCA demographic parameter GBCA* demographic parameter (or magnetic field)/ pdiff = controlu('gadobutrol') tdiff cl alpha = 0.025;
estimate "gadopiclenol – "gadobutrol" GBCA* demographic parameter (or magnetic field)1 -1 …./cl;
run; .

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 Mean, Mean + 1.96SD and Mean - 1.96SD, where Mean and SD are the mean and the SD of the difference 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 MRI modality reading;
  model BV = subject MRI modality 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 on the whole set of study patients, since each case was read by 3 different 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 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 agents 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 including the reader as covariate using the FAS2. The results will be presented overall.

Non-matching lesions

The primary analyses1 and 2 will be repeated including the non-matching lesions 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.

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 FAS 1 will include only data from the MRI using gadopiclenol .

Lesion visualization (on site read)
The same analyses as lesion visualization co-primary criteria (off-site) on matching and non-matching lesions will be performed.

Improvement in patient-level lesion visualization scores, paired versus pre-contrast images
Improvement in patient-level lesion visualization will be calculated from 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 reader, 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 or contrast agent group 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 + reader + center + error
- Internal morphology = contrast agent group + period + reader + center + error
- Degree of contrast enhancement = contrast agent group + period + reader + center + error

and the following for pre vs. paired within gadopiclenol MRI period:
- Border delineation = MRI modality + period + reader + center + error
- Internal morphology = MRI modality + period + reader + center + error
- Degree of contrast enhancement = MRI modality + period + reader + 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 eval = GBCA(or MRI modality) period reader center;
   repeated GBCA(or MRI modality) / 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% confidence intervals 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.

Lesion visualization at lesion level (off site read) by subgroup
Same analysis as above will be repeated adding
1: Body region
2: organ.

Hence the models will be the following for gadobutrol vs. gadopiclenol:
1.
• Border delineation = contrast agent group + period + reader + center + body region + error
• Internal morphology = contrast agent group + period + reader + center + body region + error
• Degree of contrast enhancement = contrast agent group + period + reader + body region + center + error

2.
• Border delineation = contrast agent group + period + reader + center + organ + error
• Internal morphology = contrast agent group + period + reader + center + organ + error
• Degree of contrast enhancement = contrast agent group + period + reader + organ + center + error

and the following for pre vs. paired within gadopiclenol MRI period:
1
• Border delineation = MRI modality + period + reader + center + body region + error
• Internal morphology = MRI modality + period + reader + center + body region + error
• Degree of contrast enhancement = MRI modality + period + reader + center + body region + error

2
• Border delineation = MRI modality + period + reader + center + organ + error
• Internal morphology = MRI modality + period + reader + center + organ + error
• Degree of contrast enhancement = MRI modality + period + reader + center + organ + 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:
1.
proc mixed data = XXX method = REML;
class lesion_# GBCA (or MRI modality) period reader center body region;
model eval = GBCA (or MRI modality) period reader center body region;
repeated GBCA (or MRI modality) / subject=lesion_# / type = cs;
/* To get the estimate and the corresponding confidence interval of the paired difference */
lsmeans GBCA (or MRI modality);
lsmeans GBCA (or MRI modality) * body region
estimate "gadopiclenol - gadobutrol" GBCA 1 -1 (or "Paired – Pre" MRI modality) /cl;
estimate "gadopiclenol - gadobutrol" GBCA (or "Paired – Pre" MRI modality) *body region … /cl;
run;

2.

```
proc mixed data = XXX method = REML;
  class lesion_# GBCA (or MRI modality)  period reader center organ;
   model eval = GBCA (or MRI modality)  period reader center organ;
   repeated GBCA (or MRI modality)  / subject=lesion_# / type = cs;
/* To get the estimate and the corresponding confidence interval of the paired difference */
   lsmeans GBCA (or MRI modality);
   lsmeans GBCA (or MRI modality) * organ
   estimate "gadopiclenol - gadobutrol" GBCA (or "Paired – Pre" MRI modality)  1 -1 /cl;
   estimate "gadopiclenol - gadobutrol" GBCA (or "Paired – Pre" MRI modality) *organ … /cl;
run;
```

The Student's t-based 95% confidence intervals of the difference between gadopiclenol and gadobutrol will be constructed for each of 3 lesion visualization criteria for each body region/organ using the FAS2 on all lesions.

Lesion size analysis for lesion visualization at lesion level (off site read)
Lesion visualization at lesion level (off site read) analysis comparing the two GBCA will be repeated with size of lesion added as co-factor. Size will be classified as following:

- =<1 cm
- >1cm and =<2 cm
- >2 cm

Hence the models will be the following:

- Border delineation = contrast agent group + period + reader + center + class_sized + error
- Internal morphology = contrast agent group + period + reader + center + class_sized + error
- Degree of contrast enhancement = contrast agent group + period + reader + center + class_sized + 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 period reader center class_sized;
   model eval = GBCA period reader center class_sized;
   repeated GBCA / subject=lesion_# / type = cs;
/* To get the estimate and the corresponding confidence interval of the paired difference */
   lsmeans GBCA;
   lsmeans GBCA* class_sized
   estimate "gadopiclenol - gadobutrol" GBCA 1 -1 /cl;
   estimate "gadopiclenol - gadobutrol" GBCA* class_sized … /cl;
run;
```

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 and 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. Matching and no matching lesions will be kept in the analysis.

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 modalities 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:
Paired vs Pre analysis in Gadopiclenol group using extended FAS1:

```
proc glimmix data = XXX;
  class subject MRI period;
    model nblesions = MRI period / 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;
```

Paired Gadopiclenol vs Paired Gadobutrol using extended FAS2:

```
proc glimmix data = XXX;
  class subject GBCA period;
    model nblesions = GBCA / 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;
```

Subgroup analyses by body region and organ as described in the section additional analysis of the primary criteria will be conducted for number of lesions.

Size of lesions
The size (largest diameter) of the 3 most representative lesions will be assessed 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 localization of the 3 most representative lesions will be assessed by off-site readers and on–site radiologists and will be displayed within each organ by contrast agent groups and MRI modalities (pre and paired); off-site and on-site reader's outcomes will be separately analyzed.
Number and percentage of patients by organ 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. One patient can have lesions in different organs and so the sum of patients by organ can be greater than the number of patients

The classification of organ will be the following:

Lesion Location	Corresponding organ
Head	Head
Right neck Left neck	Neck
Right breast Left breast	Breast
Lung	Lung
Liver Right lobe Liver Left lobe Liver Quadrate lobe Liver Caudate lobe	Liver
Gallbladder	Gallbladder
Pancreas	Pancreas
Bile ducts	Bile ducts
Spleen	Spleen
Right adrenal gland Left adrenal gland	Adrenal gland
Right kidney Left kidney	Kidney
Right urinary tract Left urinary tract	Urinary tract
Bowel	Bowel
Retroperitoneum and peritoneum	Retroperitoneum and peritoneum
Bladder	Bladder
Prostate	Prostate
Penis	Penis
Uterus	Uterus
Right ovary and Adnexae (appendages) Left Ovary and Adnexae (appendages)	Ovary
Urethra	Urethra
Right upper limb Left upper limb Right lower limb Left lower limb	Limb
Right hand Left hand	Hand
Right foot Left foot	Foot

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.

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

Diagnosis	Tumor classification
Negative	Non Malignant
Benign	Non Malignant
Probably Benign finding	Non Malignant
Low Suspicion of Malignancy	Malignant
Intermediate Suspicion of Malignancy	Malignant
Moderately High Suspicion of Malignancy	Malignant
Not assessable	Not assessable

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 / non 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 d  ddfm = kr;
  random _residual_ / subject = patient type = cs;
  estimate "gadopiclenol - gadobutrol"  GBCA -1 1 /cl;
  estimate "gadopiclenol – gadobutrol for malignant tumor" GBCA -1 1 GBCA*tumor_cl -1 0 0 1 0 0 /cl;
  estimate "gadopiclenol – gadobutrol for non malignant tumor" GBCA -1 1 GBCA*tumor_cl 0 -1 0 0 1 0/cl;
  estimate "gadopiclenol – gadobutrol for not assessable tumor" GBCA -1 1 GBCA*tumor_cl 0 0 -1 0 0 1/cl;
run;
```

Percentage Enhancement of lesions (E%)
E% is calculated from the Signal Intensity (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 FAS 2. 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 eval = 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 most representative lesions by the 3 independent off-site readers. Then, the mean of LBR will be calculated by patient and by MRI modality using only gadopiclenol-gadobutrol matching lesions. Only pre-contrast lesions which match with those gadopiclenol-gadobutrol matching lesions will be kept in the analysis and descriptive statistics.
For each reader, LBR will be tabulated by contrast agent groups on pre contrast and paired images using FAS 2.
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 eval = 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.
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 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 was tabulated for the following events :

- All AEs.
- Serious AEs (SAEs) (variable "serious" classified as yes or missing) - 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 discontinuation of the IMP.
- TEAE leading to IMP unblinding

Same analyses will be repeated by body regions.

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 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 Total column.
Same analyses will be repeated by body regions.

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 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".

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 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".

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 (HGLT), 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
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).

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

- Hematology: Red Blood Cells (RBCs), hemoglobin, hematocrit, Mean red blood Cells Volume (MCV), White Blood Cells (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, Blood Urea Nitrogen (BUN), Urea, Cystatin C, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, total bilirubin (and indirect bilirubin), conjugated bilirubin, Triglycerides, Lactate DeHydrogenase (LDH).

Quantitative analysis

Hematology and biochemistry parameters at visits 2, 3, 4 and 5 will be described as quantitative variables in both SI and conventional units as raw data and change from baseline. 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
Same analyses will be repeated by body regions.

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

Individual clinically significant abnormalities

For each hematology and chemistry parameter, number and percentage of patients with at least one clinically significant value (according to the investigator) during the trial will be presented by contrast agent groups.

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, timepoints and contrast agent groups.

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.

Injection-site tolerance will be summarized qualitatively by timepoints and contrast agent groups. Pain evaluation will be quantitatively summarized by timepoints and contrast agent groups for patient reporting pain.

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 groups 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 media groups. In this case, it will count only once in the total column

Summary table (number and % of patients) grouped by the first and the last level of ATC code will be presented for concomitant medications and will be sorted by descending frequency of the first ATC code (anatomical class) and, within each first ATC, by descending frequency of the last level of ATC code (chemical class) according to the column Total. The chemical class code will be presented along with the name in the table.

Summary table (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 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.

6.1.1. Demographic data

6.1.1.1 Disposition

Table 14.1.1.1 Patient Overall Disposition – Screened patients Set
Table 14.1.1.2 Patient Overall Disposition by Body Region – Screened patients Set
Table 14.1.1.3 Reasons for Screening Failure – Screened patients Set
Table 14.1.1.4 Reasons for Premature Discontinuation – Screened patients Set – Randomized Patients
Table 14.1.1.5 Reasons for Premature Discontinuation by body region – Screened patients Set – Randomized Patients
Table 14.1.1.6 Number of Patients by Center – Screened patients Set
Table 14.1.1.7 Patient Disposition by Visit– Screened patients Set

6.1.1.2 Protocol Deviations

Table 14.1.2.1 Major Protocol Deviations – Screened patients Set
Table 14.1.2.2 Non Major Protocol Deviations – Screened patients Set

6.1.1.3 Data Sets Analysed

Table 14.1.3.1 Analysis Data Sets: Full Analysis and Per Protocol Sets– Screened patients Set
Table 14.1.3.2 Analysis Data Sets: Safety Set – Screened patients Set

6.1.1.4 Demographics and Baseline Characteristics

Table 14.1.4.1 Demographic Data – FAS 1
Table 14.1.4.2 Demographic Data by Body Region – FAS 1
Table 14.1.4.3 Demographic Data – FAS 2
Table 14.1.4.4 Demographic Data by Body Region – FAS2
Table 14.1.4.5 Demographic Data – Safety Set
Table 14.1.4.6 Trial Disease Diagnosis According to Primary SOC and PT - FAS 1
Table 14.1.4.7 Imaging Procedure Documenting the Trial Disease - FAS 1
Table 14.1.4.8 Trial Disease Diagnosis According to Primary SOC and PT - FAS 2
Table 14.1.4.9 Imaging Procedure Documenting the Trial Disease - FAS 2
Table 14.1.4.10 Medical History According to Primary SOC and PT - FAS 1
Table 14.1.4.11 Concomitant Disease According to Primary SOC and PT - FAS 1
Table 14.1.4.12 Medical History by Body Region According to Primary SOC and PT - FAS 1
Table 14.1.4.13 Concomitant Disease by Body Region According to Primary SOC and PT - FAS 1
Table 14.1.4.14 Medical History According to Primary SOC and PT - FAS 2
Table 14.1.4.15 Concomitant Disease - According to Primary SOC and PT - FAS 2
Table 14.1.4.16 Medical History by Body Region According to Primary SOC and PT - FAS 2
Table 14.1.4.17 Concomitant Disease by Body Region - According to Primary SOC and PT - FAS 2
Table 14.1.4.18 Medical History - According to Primary SOC and PT - Safety Set
Table 14.1.4.19 Concomitant Disease According to Primary SOC and PT - Safety Set
Table 14.1.4.20 eGFR at Visit 2 and Visit 4 - Safety Set
Table 14.1.4.21 Prior Medications According to ATC first and fourth levels - FAS 1
Table 14.1.4.22 Prior Medications According to ATC first and fourth levels - FAS 2

Table 14.1.4.23 Patient's Contrast Agent Intolerance History - Safety Set

6.1.1.5 MRI Examination
Table 14.1.5.1 MRI Examination - FAS 1
Table 14.1.5.2 MRI Examination - FAS 2

6.1.1.6 Compliance with Trial product
Table 14.1.6.1 Compliance with Trial Product – FAS 1
Table 14.1.6.2 Compliance with Trial Product – FAS 2

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 – FAS 1
Table 14.2.1.2 Co-primary criteria 2 - Off-Site Readings – Mixed Model – PPS 2

Supportive Analyses of the Co-primary criteria
Table 14.2.1.3 Co-primary criteria 1 - Off-Site Readings – Mixed Model – PPS 1
Table 14.2.1.4 Co-primary criteria 2 - Off-Site Readings – Mixed Model – FAS 2

Descriptive Statistics
Table 14.2.1.5 Co-primary criteria 1- Off-Site Readings - Descriptive Statistics - FAS 1
Table 14.2.1.6 Co-primary criteria 2- Off-Site Readings - Descriptive Statistics - PPS 2
Table 14.2.1.7 Co-primary criteria 1- Off-Site Readings - Descriptive Statistics - PPS 1
Table 14.2.1.8 Co-primary criteria 2- Off-Site Readings - Descriptive Statistics – FAS 2

Assay sensitivity
Table 14.2.1.9 Lesion visualization criteria - Off-Site Readings – MRI with Gadobutrol– PAIRED vs PRE - Mixed Model - FAS 2

Subgroup analysis
Body region
Table 14.2.1.10 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE - Mixed Model adjusted by body region – FAS1
Figure 14.2.1.1 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE - Forest Plot by body region – FAS1
Table 14.2.1.11 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model adjusted by body region – FAS2
Figure 14.2.1.2 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Forest Plot by body region – FAS2
Table 14.2.1.12 Lesion visualization criteria - Off-Site Readings - MRI with Gadopiclenol– PAIRED vs PRE - Descriptive Statistics by body region – FAS1
Table 14.2.1.13 Lesion visualization criteria - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Descriptive Statistics by body region – FAS2
Organ
Table 14.2.1.14 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE - Mixed Model adjusted by organ – FAS1
Figure 14.2.1.3 Lesion visualization criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE - Forest Plot by organ – FAS1

Additional Analyses of the Primary Criterion

Intra- Off-Site Reader Variability

Inter- Off-Site Reader Variability

Global model

Presentation of number of patients and number of lesions

Non-matching lesions

Drop-out patients

Meta-readers analysis:

Table 14.2.1.41 Lesion visualization criteria - Off-Site Readings from Meta-readers – Descriptive Statistics – MRI with Gadopiclenol vs MRI with Gadobutrol - FAS 2
Table 14.2.1.42 Lesion visualization criteria - Off-Site Readings from Meta-readers – MRI with Gadobutrol – PAIRED vs PRE - Mixed Model - FAS 2

Normality assessment of the primary analyses
Figure 14.2.1.19 Lesion visualization criteria - Off-Site Readings – Normal Probability Plots – FAS 1
Figure 14.2.1.20 Lesion visualization criteria - Off-Site Readings – Normal Probability Plots – PPS 2

6.1.2.2 Secondary Efficacy Criteria

Lesion visualization on site evaluation

Table 14.2.2.1 Lesion visualization criteria - On-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE – Mixed Model – Extended FAS 1
Table 14.2.2.2 Lesion visualization criteria - On-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model – Extended FAS 2
Table 14.2.2.3 Lesion visualization criteria - On-Site Readings - MRI with Gadopiclenol– Descriptive Statistics – Extended FAS 1
Table 14.2.2.4 Lesion visualization criteria - On-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Descriptive Statistics – Extended FAS 2
Table 14.2.2.5 Lesion visualization criteria - On-Site Readings – Mixed Model – MRI with Gadobutrol – PAIRED vs PRE - Extended FAS 2

Improvement in patient-level lesion visualization scores, paired versus pre-contrast images
Table 14.2.2.6 Improvement in patient-level lesion visualization scores - Off-Site Readings– MRI with Gadopiclenol- FAS 1
Table 14.2.2.7 Improvement in patient-level lesion visualization scores - Off-Site Readings– MRI with Gadobutrol– FAS 2
Table 14.2.2.8 Improvement in patient-level lesion visualization scores - On-Site Readings – MRI with Gadopiclenol – Extended FAS 1
Table 14.2.2.9 Improvement in patient-level lesion visualization scores - On-Site Readings – MRI with Gadobutrol – Extended FAS 2

Lesion visualization at lesion level
Table 14.2.2.10 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol – PAIRED vs PRE –– Mixed Model – Extended FAS 1
Table 14.2.2.11 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol –– Mixed Model – Extended FAS 2
Table 14.2.2.12 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol – PAIRED vs PRE –– Mixed Model adjusted by body region– Extended FAS 1
Table 14.2.2.13 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol –– Mixed Model adjusted by body region– Extended FAS 2
Figure 14.2.2.1 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol - PAIRED vs PRE –– Forest Plot by body regions – Extended FAS 1
Figure 14.2.2.2 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Forest Plot by body regions – Extended FAS 2
Table 14.2.2.14 Lesion visualization criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol - PAIRED vs PRE –– Mixed Model adjusted by organ – Extended FAS 1

Lesion size analysis for lesion visualization at lesion level (off site read)

Technical Adequacy of Images

Lesion Detection Capacity: Number, Size and Location of Lesions

Number of Lesions

Table 14.2.2.33 Number of Lesions by body region - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – Extended FAS 2
Table 14.2.2.34 Number of Lesions by organ - Off-Site Readings – MRI with Gadopiclenol - PAIRED vs PRE - Negative Binomial Regression Model - Extended FAS 1
Figure 14.2.2.7 Number of Lesions - Off-Site Readings – Forest Plot by organ – MRI with Gadopiclenol PAIRED vs PRE - Extended FAS 1
Table 14.2.1-35 Number of Lesions by organ - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – – Negative Binomial Regression Model – Extended FAS 2
Figure 14.2.2.8 Number of Lesions - Off-Site Readings – Forest Plot by organ – MRI with Gadopiclenol vs MRI with Gadobutrol –Extended FAS 2
Table 14.2.1-36 Number of Lesions by organ - Off-Site Readings - MRI with Gadopiclenol - Descriptive Statistics –Extended FAS 1
Table 14.2.1-37 Number of Lesions by organ - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – Extended FAS2

Size of Lesions

Table 14.2.2.38 Largest Diameter of Lesions Detected - Off-Site Readings – MRI with Gadopiclenol – Extended FAS 1
Table 14.2.2.39 Largest Diameter of Lesions Detected - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2
Table 14.2.2.40 Largest Diameter of Lesions Detected - On-Site Reading – MRI with Gadopiclenol - Extended FAS 1
Table 14.2.2.41 Largest Diameter of Lesions Detected - On-Site Reading – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2

Location of Lesions

Table 14.2.2.42 Location of Lesions Detected - Off-Site Readings - MRI with Gadopiclenol - Extended FAS 1
Table 14.2.2.43 Location of Lesions Detected - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2
Table 14.2.2.44 Location of Lesions Detected - On-Site Reading - MRI with Gadopiclenol - Extended FAS 1
Table 14.2.2.45 Location of Lesions Detected - On-Site Reading - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2

Level of Diagnostic Confidence

Table 14.2.2.46 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings - MRI with Gadopiclenol - Extended FAS 1
Table 14.2.2.47 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2
Table 14.2.2.48 Radiological Diagnosis and Level of Diagnostic Confidence - On-Site Reading – MRI with Gadopiclenol - Extended FAS 1
Table 14.2.2.49 Radiological Diagnosis and Level of Diagnostic Confidence - On-Site Reading – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2

Impact on Patient treatment Plan

Table 14.2.2.50 Patient Treatment Plan Evaluation - On-Site Reading - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2

Table 14.2.2.51 Patient Treatment Plan Evaluation by tumor classification before GBCA administration - On-Site Reading - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2
Table 14.2.2.52 Patient Treatment Plan Evaluation by tumor classification before GBCA administration - On-Site Reading - Gadopiclenol vs Gadobutrol – MRI with Gadopiclenol vs MRI with Gadobutrol – Logistic Regression - Extended FAS 2

Signal intensity
Table 14.2.2.53 Percentage of enhancement - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – FAS 2
Table 14.2.2.54 Percentage of enhancement - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Mixed Model – FAS 2
Table 14.2.2.55 Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – FAS 2
Table 14.2.2.56 Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Mixed Model – FAS 2

Overall Diagnostic Preference
Table 14.2.2.57 Overall Diagnostic Preference and Reason - Off-Site Readings - Extended FAS 2

6.1.3. Safety data

6.1.3.1 Extent of exposure
Table 14.3.1.1 Summary of Trial Participation Duration – Safety Set
Table 14.3.1.2 Trial Contrast Agent Administration Modalities – Safety Set

6.1.3.2 Adverse events
Table 14.3.2.1 Non-Treatment Emergent Adverse Events –Overview – Screened patients Set
Table 14.3.2.2 Treatment Emergent Adverse Events –Overview – Safety Set
Table 14.3.2.3 Treatment Emergent Adverse Events –Overview by Body Region – Safety Set
Table 14.3.2.4 Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Set
Table 14.3.2.5 Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term by Body Region – Safety Set
Table 14.3.2.6 Treatment Emergent Adverse Events with Causal Relationship to IMP by Primary System Organ Class and Preferred Term – Safety Set
Table 14.3.2.7 Treatment Emergent Adverse Events with Causal Relationship to a Trial Procedure by Primary System Organ Class and Preferred Term – Safety Set

6.1.3.3 Deaths, serious adverse events and other significant adverse events
Table 14.3.2.8 Listing of Deaths - Safety Set
Table 14.3.3.9 Listing of Serious Adverse Events other than Deaths - Safety Set
Table 14.3.3.10 Listing of Adverse Events of Special Interest other than Serious Adverse Events - Safety Set

6.1.3.4 Laboratory data
Table 14.3.3.1 Hematology Data - Raw data and Change from Baseline – SI Units – Safety Set

Table 14.3.3.2 Hematology Data - Raw data and Change from Baseline – Conventional US Units – Safety Set
Table 14.3.3.3 Biochemistry Data - Raw data and Change from Baseline – SI Units – Safety Set
Table 14.3.3.4 Biochemistry Data - Raw data and Change from Baseline – Conventional US Units – Safety Set
Table 14.3.3.5 Hematology Data - Raw data and Change from Baseline by Body Region – SI Units – Safety Set
Table 14.3.3.6 Hematology Data - Raw data and Change from Baseline by Body Region – Conventional US Units – Safety Set
Table 14.3.3.7 Biochemistry Data - Raw data and Change from Baseline by Body Region – SI Units – Safety Set
Table 14.3.3.8 Biochemistry Data - Raw data and Change from Baseline by Body Region – Conventional US Units – Safety Set
Table 14.3.3.9 Shift Table of Serum Creatinine, eGFR, BUN and Cystatin C between Baseline Measurement and Post-Injection Measurement – SI units – Safety Set
Table 14.3.3.10 Shift Table of Serum Creatinine, eGFR, BUN and Cystatin C between Baseline Measurement and Post-Injection Measurement – Conventional US units – Safety Set

6.1.3.5 Vital Signs, physical findings and other observations related to safety

Vital signs

Table 14.3.4.1 Vital Signs – Raw data and Change from Baseline – Safety Set

Other observations

Table 14.3.4.2 Injection Site Tolerance – Safety Set
Table 14.3.4.3 Patient Pain Evaluation - Safety Set

6.1.3.6 Concomitant therapies

Table 14.3.4.4 Concomitant Medications according to ATC System Main Group anatomical class and chemical class –Safety Set
Table 14.3.4.5 Concomitant procedures by Primary System Organ Class and Preferred Term – Safety Set

6.2. Contents of clinical study report section 16.2

6.2.1. Disposition (Section 16.2.1 of ICH Report)

Listing 16.2.1.1 Final Status - Screened patients Set
Listing 16.2.1.2 Trial Premature Discontinuation for Patients not Completing the Trial- Screened patients Set
Listing 16.2.1.3 Visit Dates - Screened patients Set
Listing 16.2.1.4 Inclusion Criteria Not Respected - Screened patients Set
Listing 16.2.1.5 Non Inclusion Criteria Not Respected - Screened patients Set

6.2.2. Protocol Deviations (Section 16.2.2 of ICH Report)

Listing 16.2.2.1 Major Protocol Deviations - Screened patients Set
Listing 16.2.2.2 Non Major Protocol Deviations - Screened patients Set

6.2.3. Subjects Excluded from Efficacy Analysis (Section 16.2.3 of ICH Report)

Listing 16.2.3.1 Analysis Data Sets - Screened patients Set

6.2.4. Demographic Data and Baseline Characteristics (Section 16.2.4 of ICH Report)

Listing 16.2.4.1 Demographics - Screened patients Set
Listing 16.2.4.2 Patient Intolerance to Contrast Agent History - Screened patients Set
Listing 16.2.4.3 Medical History - Screened patients Set
Listing 16.2.4.4 Trial Disease Diagnosis - Screened patients Set
Listing 16.2.4.5 Physical Examination - Screened patients Set
Listing 16.2.4.6 Pregnancy Test - Screened patients Set
Listing 16.2.4.7 Prior and Concomitant Medications - Screened patients Set
Listing 16.2.4.8 Concomitant Procedures - Screened patients Set

6.2.5. Compliance and/or Drug Concentration Data (Section 16.2.5 of ICH Report)

Listing 16.2.5.1 MRI Examination - Screened patients Set
Listing 16.2.5.2 Summary of Durations in the Study - Screened patients Set
Listing 16.2.5.3 Compliance Data – Screened patients Set
Listing 16.2.5.4 Trial Contrast Agent Administration Modalities - Screened patients Set

6.2.6. Individual Efficacy Response Data (Section 16.2.6 of ICH Report)

6.2.6.1 Primary Efficacy Co primary criteria

Listing 16.2.6.1 Lesion visualization criteria - Off-Site Readings - Reader #1 - Screened patients Set
Listing 16.2.6.2 Lesion visualization criteria - Off-Site Readings - Reader #2 - Screened patients Set
Listing 16.2.6.3 Lesion visualization criteria - Off-Site Readings - Reader #3 - Screened patients Set

6.2.6.2 Secondary Efficacy Criteria

Listing 16.2.6.4 Lesion visualization criteria - On-Site Readings - Screened patients Set
Listing 16.2.6.5 Technical Adequacy and Number of Lesions- Off-Site Readings - Reader #1 - Screened patients Set
Listing 16.2.6.6 Technical Adequacy and Number of Lesions - Off-Site Readings - Reader #2 - Screened patients Set
Listing 16.2.6.7 Technical Adequacy and Number of Lesions - Off-Site Readings - Reader #3 - Screened patients Set
Listing 16.2.6.8 Technical Adequacy and Number of Lesions - On-Site Reading - Screened patients Set
Listing 16.2.6.9 Lesions: Location and Largest Diameter - Off-Site Readings - Reader #1 - Screened Patients Set
Listing 16.2.6.10 Lesions: Location and Largest Diameter - Off-Site Readings - Reader #2 - Screened Patients Set

Listing 16.2.6.11 Lesions: Location and Largest Diameter - Off-Site Readings - Reader #3 - Screened Patients Set
Listing 16.2.6.12 Lesions: Location and Largest Diameter - On-Site Readings - Screened Patients Set
Listing 16.2.6.13 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings - Reader #1 - Screened patients Set
Listing 16.2.6.14 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings - Reader #2 - Screened patients Set
Listing 16.2.6.15 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings - Reader #3 - Screened patients Set
Listing 16.2.6.16 Radiological Diagnosis and Level of Diagnostic Confidence - On-Site Reading - Screened patients Set
Listing 16.2.6.17 Patient Treatment Plan Evaluation - On-Site Reading - Screened patients Set
Listing 16.2.6.18 Signal Intensity Measurements - Off-Site Readings - Reader #1 - Screened patients Set
Listing 16.2.6.19 Signal Intensity Measurements - Off-Site Readings - Reader #2 - Screened patients Set
Listing 16.2.6.20 Signal Intensity Measurements - Off-Site Readings - Reader #2 - Screened patients Set
Listing 16.2.6.21 Overall Diagnostic Preference and Reason - Off-Site Readings – Reader #4 - Screened patients Set
Listing 16.2.6.22 Overall Diagnostic Preference and Reason - Off-Site Readings – Reader #5 - Screened patients Set
Listing 16.2.6.23 Overall Diagnostic Preference and Reason - Off-Site Readings – Reader #6 - Screened patients Set

6.2.7. Adverse Event Listings (Section 16.2.7 of ICH Report)

Listing 16.2.7.1 Adverse Events of Not Treated Patients or Occurring Prior to the First Injection of Contrast Agent - Screened patients Set
Listing 16.2.7.2 Adverse Events Occurring After the First Injection of Contrast Agent - Screened patients Set

6.2.8. Listing of Individual Laboratory Measurements (Section 16.2.8 of ICH Report)

Listing 16.2.8.1 Hematology - SI Units - Screened patients Set
Listing 16.2.8.2 Hematology - Conventional Units - Screened patients Set
Listing 16.2.8.3 Biochemistry - SI Units - Screened patients Set
Listing 16.2.8.4 Biochemistry - Conventional Units - Screened patients Set
Listing 16.2.8.5 Hematology – Unscheduled - SI Units - Screened patients Set
Listing 16.2.8.6 Hematology - Unscheduled - Conventional Units - Screened patients Set
Listing 16.2.8.7 Biochemistry - Unscheduled - SI Units - Screened patients Set
Listing 16.2.8.8 Biochemistry - Unscheduled - Conventional Units - Screened patients Set
Listing 16.2.8.9 Hematology and Biochemistry – Reason Test Not Done - Screened patients Set

6.2.9. Vital Signs, Physical Findings and Other Observations Related to Safety

Listing 16.2.9.1 Vital Signs - Screened patients Set
Listing 16.2.9.2 Vital Signs – Further measurements - Screened patients Set
Listing 16.2.9.3 Vital Signs Not Done - Screened patients Set
Listing 16.2.9.4 Injection Site Tolerance - Screened patients Set

7. REFERENCES

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2. EMA. Guideline on the choice of the non-inferiority margin. https://www.ema.europa.eu/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

8. APPENDICES