STATISTICAL ANALYSIS PLAN No GDX-44-014 / GDX-101

EFFICACY AND SAFETY OF GADOPICLENOL FOR MAGNETIC RESONANCE IMAGING (MRI) IN JAPANESE ADULTS AND CHILDREN

Phase III clinical study

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HISTORY FORM

Version	Date	Reason for change
1.0	2 January 2024	
2.0		Minimum number of pediatric patients to be recruited per age group and in PK cohort is alleviated The non-inclusion criterion for patients referred for contrast-enhanced cardiac MRI was modified. For the adult cohort, the set pooling all randomized patients is not used and so removed. For the pediatric cohort, both PP set and PK set are not used and removed. Improvement in lesion visualization scores at patient-level will not be analyzed. Difference between combined enhanced-unenhanced and unenhanced for lesion visualization criteria will not be analyzed on the PPS in addition on the FAS. Sensitivity analyses will not be performed on the FAS in addition on the PPS. For the pediatric cohort, the overall disposition will not be presented by age group but only by indication. The same for the number of patients by site that will be presented only overall and no longer by age group. For the pediatric cohort, the inter-reader variability will be analysed on the FAS instead of the PPS as all efficacy analyses are performed using the FAS. The location of lesions and the Patient treatment plan will be only listed. For the adult cohort, the safety parameters (AE, laboratory data and vital signs) will be presented by indication (CNS and Body) instead of body regions. For both adult and pediatric cohort, no qualitative analysis will be performed for vital signs and ECG. The classification Important/non important has been added for all protocol deviations. Protocol deviations related to the IMP injection will be presented in the same category whatever it is for gadobutrol or gadopiclenol.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body Weight
CC	Cholangiocellular Carcinoma
CI	Confidence Interval
CNR	Contrast to Noise ratio
CNS	Central Nervous System
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DCIS	Ductal Carcinoma In Situ
E%	Percentage Enhancement of lesion
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FNH	Focal nodular hyperplasia
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
GEE	General Estimating Equation
HA	Hepatic Adenoma
HCC	Hepatocellular Carcinoma
HLGT	High-Level Group Term
HLT	High-Level Term
ICC	Intra-Class Correlation
ICF	Inform Consent Form
ICH	International Conference on Harmonization
IDC	Invasive Ductal Cancer
ILC	Invasive Lobular Carcinoma
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
LBR	Lesion to Background Ratio
LCIS	Lobular Carcinoma In-Situ
LDH	Lactate Dehydrogenase
LLT	Lower Level Term
MCV	Mean red blood Cells Volume
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NSF	Nephrogenic Systemic Fibrosis
NTEAE	Non-treatment emergent Adverse Event
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SE	Standard Error
SOC	System organ Class
SOT	Standard of Truth
SPS	Screened Patient Set
SS	Safety Set
TEAE	Treatment Emergent Adverse Event

TABLE OF CONTENTS

1. SUMMARY OF THE TRIAL PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet/Bracco phase III clinical trial, Protocol No. GDX-44-014/GDX-101: "Efficacy and safety of gadopiclenol for Magnetic Resonance Imaging (MRI) in Japanese adults and children".

This analysis plan is based on the final protocol Version 5.0 dated 22October 2024.

1.1. Trial objectives

Primary objective – Adult patients only:
To demonstrate the non-inferiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to gadobutrol enhanced MRI at 0.1 mmol/kg BW in terms of lesion visualization in Japanese adult patients referred for contrast-enhanced MRI of Central Nervous System (CNS) or Body regions.

Secondary objectives for adult patients:
- To demonstrate the superiority of gadopiclenol-enhanced MRI compared to unenhanced MRI in terms of lesion visualization.
- To evaluate the efficacy of gadopiclenol-enhanced MRI per indication (CNS, Body)
- To evaluate the efficacy of gadopiclenol-enhanced MRI per subgroup of body regions and per organ (if number of patients permits evaluation).
- To evaluate the efficacy of gadopiclenol-enhanced MRI based on quantitative parameters.
- To evaluate the safety of gadopiclenol at 0.05 mmol/kg BW and gadobutrol at 0.01mmol BW based on clinical and biological parameters.

Secondary objectives for pediatric patients:
- To evaluate the efficacy of gadopiclenol-enhanced MRI compared to unenhanced MRI in terms of lesion visualization.
- To evaluate the safety in pediatric patients of gadopiclenol based on clinical including electrocardiogram (ECG) and biological parameters.

Secondary objective for pediatric patients – Pharmacokinetics (PK) group
- To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection in a subgroup of pediatric patients referred for contrast-enhanced MRI of CNS or Body regions.

Secondary objectives for all patients:
- To evaluate the diagnostic performance (sensitivity, specificity) of gadopiclenol-enhanced MRI for malignancy in patients with an available standard of truth (based on histopathology results and other clinical information).
- To evaluate the efficacy of gadopiclenol-enhanced MRI based on additional qualitative parameters.

1.2. Trial design

This national trial conducted in Japan includes 2 different cohorts of patients: adult patients and pediatric patients, with two different designs.
- The cohort of adult patients has a prospective, multicenter, randomized, double-blind, controlled and cross-over design.
- The cohort of pediatric patients has a prospective, multicenter, non-randomized, open-label and single arm design.

Adult cohort
Adult patients will perform a screening visit (V1), then will be randomly assigned in a 1:1 ratio to one of 2 sequences of contrast-enhanced MRI examinations: with gadopiclenol for the first MRI at V2 and then gadobutrol for the second MRI at V4 or vice-versa. 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. For patients who undergo a biopsy or a surgery of an imaged lesion within 30 days after the last MRI examination, results of histopathology (patient's diagnosis) will be recorded.
Two hundred (200) patients will be included. Inclusion will follow the rule below:

- at least 80 patients referred for CNS MRI.
- at least 80 patients referred for Body region MRI among them at least:
    - 20 patients referred for thorax MRI,
    - 25 patients referred for abdomen MRI,
    - 10 patients referred for pelvis MRI,
    - 5 patients referred for musculoskeletal system MRI,
    - other 20 patients can be referred for any Body MRI including head and neck indication.
- Other 40 patients can be referred for CNS or any Body region MRI.

The images will be assessed off-site by 3 independent blinded radiologists per anatomical region for the reading of unpair images and by 3 additional independent blinded radiologists for the global pairs assessment. Independent blind radiologists will be assigned to CNS or any Body regions according to their expertise. Furthermore, to allow exact matching of lesions between imaging modalities i.e. between unenhanced MRI (pre) and combined unenhanced and contrast enhanced MRI (paired) of each contrast agent and between paired of both contrast agents, an independent radiologist will perform lesion tracking. In addition, the images will be assessed on-site.

Pediatric cohort
Forty (40) patients will be included. The inclusions will be shared into 4 groups: patients from birth to 23 months of age inclusive, young children from 2 to 6 years of age, preadolescents from 7 to 11 years of age and adolescents from 12 to 17 years of age.
Pediatric patients will perform a screening visit (V1), then will do an MRI with gadopiclenol visit (V2) followed by a safety visit (V3) performed 1 day after the MRI visit. For patients who undergo a biopsy or a surgery of an imaged lesion within 30 days after the last MRI examination, results of histopathology (patient's diagnosis) will be recorded.

- Inclusion will follow the rule below:
- Within each group of age from 2 to 17 years, at least:
    - 2 patients referred for CNS MRI,
    - 2 patients referred for Body region MRI,
    - other patients can be referred for CNS or Body region MRI.

The images will be assessed on-site by the same investigator at each participating hospital and off-site by 3 independent blinded radiologists for the reading of unpair images. Independent blind radiologists will be assigned to CNS or any Body regions according to their expertise. Furthermore, to allow exact matching of lesions between imaging modalities (Pre and Paired), an independent radiologist (lesion tracker) will perform lesion tracking.

Up to twenty-four (24) patients of the pediatric cohort will be included in the subgroup of PK profile assessment.

Standard of truth (SOT) is defined as either the results of histopathology of a biopsy or a surgery of an imaged lesion or the assessment of the clinical information available.

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

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

For the pediatric cohort, age is expressed in months and calculated as follow:

- For patients older than 2 years old by multiplying by 12 the age collected in years and adding the age collected in month
- For patients younger than 2 years old by subtracting date of first IMP injection to the date of birth and taking the integer of the difference expressed in month.

For the adult cohort, age is expressed in year.

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

For adult cohort, age will be categorized as follow: <65 and ≥65 years.

Other baseline characteristics are:

- Trial target lesion(s) diagnosis
- Imaging procedure documenting the trial target lesion(s) diagnosis
- Medical history and concomitant diseases
- Serum creatinine and estimated Glomerular Filtration Rate (eGFR)
- Patient history of previous contrast agent exposure
- Prior medications
- MRI examination parameters.

Time between imaging procedure documenting the trial target lesion 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.

Trial target lesion(s) diagnosis, medical history and concomitant diseases will be coded in System Organ Classes (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version at the time of the database lock.

Medical histories are the ones flagged as "Not Ongoing" and concomitant diseases are those flagged as "Ongoing" at the screening visit.

Serum creatinine and eGFR are collected locally along with the eGFR method at screening visit for all patients. For pediatric patients, age-adjusted eGFR normal ranges are collected as well. For adult patients, local serum creatinine and eGFR collected locally at screening are used only to check the eligibility of the patient and are not used for safety analysis. For pediatric patients, local serum creatinine and eGFR collected locally at screening are used both to check the eligibility and for safety analysis.

Prior medications are defined as medications ended before the first administration and will be coded using the B3 WHO Drug Global version at the time of the database lock

2.2. Efficacy criteria

2.2.1. Primary criterion

The primary criterion of the trial is lesion visualization assessed off-site on paired (unenhanced and contrast-enhanced) images acquired with gadopiclenol and gadobutrol on adult patients.

The lesion visualization is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement.

- 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

For each co-primary criterion, a mean of scores will be calculated for each patient as follows:
Mean of scores = (score of lesion 1 + score of lesion 2 (if any) + score of lesion 3 (if any) + …) divided by the number of lesions (up to 10 largest and most enhancing lesions).

2.2.2. Secondary efficacy Criteria

Lesion visualization criteria

- on Paired images assessed off site for pediatric patients,
- on Pre images assessed off site for all patients,
- on Pre and Paired images assessed on site for all patients.

Definitions of each criterion and score calculation are provided in section 2.2.1

Technical adequacy of images

The off-site scanned body region is collected for each reader and could be different from the body region on-site for which the MRI has been done and between readers.
For each contrast agent, images will be evaluated on-site and off-site for adult and pediatric patients as technically adequate for diagnosis.

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

1 = Non diagnostic
2 = Poor
3 = Fair
4 = Good

If non-diagnostic, the reasons are provided:

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

If the technical adequacy of images is rated as “Non Diagnostic” then the image will be considered as not assessable.

Number of lesions

For adult patients, number of lesions will be counted for each contrast agent in a global matched-pairs fashion. For pediatric patients, number of lesions will be counted for gadopiclenol by unpaired image set (pre and paired MRI).
Investigator will record either > 10 or exact number when ≤ 10 lesions

Lesion detectability

Up to 10 lesions per patient will be tracked between MRI modalities and contrast agents allowing a cross tabulation between contrast agents for adult patients and between MRI modalities for pediatric patients. For patients with more than 10 lesions, all lesions will not be tracked and thus these patients will not be included in the analyses.

Size and location of lesions

The size (largest diameter) and location of the 10 largest and most enhancing lesions will be recorded on-site and off-site for adult and pediatric patients at unpaired image sets.

Patient’s diagnosis

The final patient diagnosis will be reported for all patients for whom technical adequacy of images is not rated "Non Diagnostic" (adult and pediatric), on-site for each contrast agent on Pre and Paired unpaired images, off-site for each contrast agent on Pre and Paired unpaired images and by the SOT if any.

Confidence in diagnosis will be reported each time a diagnosis is done except for the SOT.

Diagnosis will be chosen from the following:

For patients referred for CNS MRI:

- Non-Tumor
  - Inflammatory disease (including multiple sclerosis)
  - Infectious diseases
  - Not determined
  - Other
- Benign tumor
  - Gliomas (Low grade WHO grade I and II)
  - Pituitary adenoma
  - Meningiomas
  - Pineal tumors

  - Craniopharyngioma
  - Cranial and paraspinal nerve tumors
  - Not determined
  - Other
- Malignant tumor
  - Metastases
  - Gliomas (High grade)
  - Lymphomas
  - Embryonal tumors
  - Not determined
  - Other

For patients referred for Head and Neck MRI:

- Non-tumor:
  - Inflammation (including sinusitis, abscess)
  - Not determined
  - Other
- Benign tumor:
  - Adenoma
  - Fibroma
  - Not determined
  - Other
- Malignant tumor:
  - Carcinoma
  - Not determined
  - Other

For patients referred for Breast MRI

- Non-Tumor:
  - Inflammation/ Infection (e.g., mastitis)
  - Mastopathy
  - Not determined
  - Other

- Benign tumor:
  - Fibroadenoma,
  - Papilloma
  - Not determined
  - Other

- Malignant tumor:
  - Invasive ductal cancer (IDC)
  - Invasive lobular carcinoma (ILC)
  - Ductal Carcinoma In Situ (DCIS)
  - Lobular Carcinoma In-Situ (LCIS)
  - Not determined
  - Other

For patients referred for Lung MRI

- Non-Tumor:
  - Fibrosis
  - Inflammation/Infection (e.g., pneumonia, abscess, emphysema)

  - Not determined
  - Other

- Benign tumor:
  - Adenoma
  - Pulmonary hamartoma
  - Pulmonary papilloma
  - Not determined
  - Other

- Malignant tumor:
  - Metastases
  - Primary cancer
  - Not determined
  - Other

For patients referred for Liver MRI

- Non-Tumor:
  - Not determined
  - Other

- Benign tumor:
  - Hemangioma
  - Focal nodular hyperplasia (FNH)
  - Hepatic adenoma (HA)
  - Abscess
  - Not determined
  - Other

- Malignant tumor:
  - Hepatocellular carcinoma (HCC)
  - Cholangiocellular Carcinoma (CC)
  - Metastasis
  - Not determined
  - Other

For patients referred for Pancreas MRI

- Non-Tumor:
  - Pancreatis
  - Not determined
  - Other

- Benign tumor:
  - Pancreatic pseudocyst
  - Pancreatic Serous cystadenoma
  - Not determined
  - Other

- Malignant tumor:
  - Cancer
  - Not determined
  - Other

For patients referred for Kidneys and urinary tract MRI

- Non-Tumor:
  - Hydronephrosis/ Inflammation/ Infection
  - Not determined
  - Other

- Benign tumor:
  - Renal adenoma
  - Oncocytoma
  - Angiomyolipoma
  - Not determined
  - Other

- Malignant tumor:
  - Renal carcinoma
  - Not determined
  - Other

For patients referred for Prostate MRI

- Non-Tumor:
  - Inflammation
  - Not determined
  - Other

- Benign tumor:
  - Adenoma
  - Not determined
  - Other

- Malignant tumor:
  - Prostate Cancer
  - Not determined
  - Other

For patients referred for Uterus, uterine appendages and ovary MRI

- Non-Tumor:
  - Endometriosis
  - Inflammation/ Infection (including abscess)
  - Not determined
  - Other

- Benign tumor:
  - Uterine myoma
  - Not determined
  - Other

- Malignant tumor:
  - Endometrial carcinoma
  - Uterine leiomyosacromas
  - Not determined

- Other

For patients referred for Musculo-Skeletal MRI

- Non-Tumor:
  - Inflammation (e.g., rheumatic disease, synovitis, osteitis, chondritis)
  - Infection (e.g., abscess)
  - Not determined
  - Other

- Benign tumor:
  - Fibroma
  - Chondroma
  - Hemangioma
  - Not determined
  - Other

- Malignant tumor:
  - Metastases
  - Sarcoma
  - Not determined
  - Other

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

1 = Nil: very uncertain
2 = Poor: uncertain
3 = Moderate: moderately certain
4 = High: good certainty
5 = Excellent: very certain

Patient management plan

Prediction of change in the patient management will be assessed on-site for adult patients on global matched pairs.

Signal intensity parameters

For each contrast agent, signal intensity will be measured off-site for adult patients on global matched pairs for up to 3 common largest and most homogeneously enhancing lesions.

Contrast to Noise ratio (CNR) will be calculated in patients referred for CNS MRI only, on Pre contrast and Paired images as follow:

CNR = (SI_lesion - SI_ht)/ SD_noise

where SI_lesion = Signal intensity of lesion
SI_ht = Signal intensity of healthy tissue
SD_noise = Standard Deviation (SD) of background noise

Percentage enhancement (E%) of lesion(s) will be calculated as follow:

E% = (SI_post - SI_pre)/ SI_pre x100

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) will be calculated on Pre contrast and Paired images as follow:

LBR =SI_lesion/SI_b

where SI_lesion = Signal intensity of lesion
SI_b= Signal intensity of surrounding healthy tissue of the lesion.

The 3 quantitative criteria (CNR, E%, LBR) will be then calculated at patient level, when applicable, in averaging the parameter for maximum 3 lesions.

Overall diagnostic preference
The evaluation will be performed off-site only for adult patients in a global matched-pairs fashion and the assessment will be performed based on 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
  If chosen, the readers will need to indicate whether this would impact patient management or not.
  If no, at least one answer is required:
  - potentially non malignant lesion to be left untouched,
  - potentially non malignant lesion to be at best followed up,
  - potential malignant lesion in a clinical situation when number do not matter any longer,
  - other reasons that had to be specified.

  If yes, the rational is required (Free text)
- Diagnostic confidence was greater
  If yes at least one answer is required:
  - detection of lesions,
  - characterization of disease,
  - assignment of a grade to disease,
  - definition of extent of disease,
  - other reasons that had to be specified.

2.3. Safety criteria

2.3.1. Extent of Exposure

Extent of exposure will be described by a summary of durations in the study and a display of study contrast agent administration modalities.

The study contrast agent administration modalities are the following parameters:

- Investigational Medicinal Product (IMP) administered (Yes/No)
- Overdose occurred (Yes/No)
- Mode of injection (Manual/Power injector/Power injector name)
- Injection rate (mL/s)
- Injection site (Peripheral vein of the antecubital region, Dorsal arch of the hand, Dorsal arch of the feet, Other)
- Injection of saline flush (yes/no)
- Volume of contrast agent actually administered (mL)

The patient's theoretical dose of contrast agent is calculated based on his/her weight. The difference between theoretical and actual dose in mL and in % will be calculated:

Difference (mL) = Volume actually administered (mL) – Theoretical calculated volume (mL)

$$Difference\ (\%) = \frac{Volume\ actually\ administered\ (mL) - theoretical\ calculated\ volume\ (mL)}{theoretical\ calculated\ \ volume\ (mL)} * 100$$

The study participation durations for the adult cohort are as follows:

- Duration between the GBCA injection and either the following GBCA injection (if any) or the end of study (in days): date of the end of study – date of last GBCA injection + 1 and date of the 2nd GBCA injection - date of the 1st GBCA injection.

The study participation durations for the pediatric cohort are as follows:

- Duration between the gadopiclenol injection and the end of study (in days): date of the end of study – date of gadopiclenol injection + 1

2.3.2. Adverse Events

Adverse Events will be recorded throughout patient's participation. AEs will be coded using MedDRA dictionary version at the time of the database lock.
A serious AE is defined as an event with seriousness classified as "Yes"
An Adverse Event of Special Interest (AESI) for this protocol is defined by suspected or confirmed Nephrogenic Systemic Fibrosis (NSF). The MedDRA code 10067467 corresponding to the PT "Nephrogenic systemic fibrosis" will be used to identify these AESI.
AEs with causal relationship to the IMP are those described by the investigator with causal relationship to the IMP "related".
AEs with causal relationship to a trial procedure are those described by the investigator with causal relationship to a trial procedure "related".

AEs emergence will be defined as follows:

- Non-treatment emergent AE (NTEAE): if the AE starts prior to the first IMP administration for adult cohort and prior to the IMP administration for pediatric cohort or if the patient is not injected.
- Treatment emergent AE (TEAE): if the AE starts after first IMP administration for adult cohort and after the IMP administration for pediatric cohort.

If an AE start date is missing or unknown, the AE will be considered as treatment emergent.
Time to onset of AE will be calculated as follow: datetime of AE onset – datetime of IMP administration.
If the AE start date is missing or unknown, it will be imputed as the first treatment administration date.
When the start date of an AE is only partially known, it will be imputed so that the time to onset is minimal.

2.3.3. Clinical laboratory evaluation

Blood samples for adult patients will be collected centrally according to the following schedules:

- The day of each contrast agent injection before the administration (baseline value is from the last samples collected prior to the first agent injection)
- one day after each contrast agent injection

Blood samples for pediatric patients will be collected locally according to the following schedules:

- The day of screening (baseline value)
- one day after the contrast agent injection

The following tables list, in order of presentation, all parameters in standard international units (SI):

Hematology parameters	**SI Units**
Erythrocytes (Red Blood cells)	10^{12}/L
Hemoglobin	g/L
Hematocrit	L/L
Mean red blood Cells volume (MCV)	fL
Leukocytes (White Blood cells)	10^9/L
Neutrophils	10^9/L
Neutrophils/Leukocytes	%
Lymphocytes	10^9/L
Lymphocytes/Leukocytes	%
Monocytes	10^9/L
Monocytes/Leukocytes	%
Eosinophils	10^9/L
Eosinophils/Leukocytes	%
Basophils	10^9/L
Basophils/Leukocytes	%
Platelet count	10^9/L

Biochemistry parameters	**SI Units**
Sodium	mmol/L
Potassium	mmol/L
Chloride	mmol/L
Blood Urea Nitrogen (BUN)	mmol/L
Urea*	mmol/L
Total protein	g/L
Calcium	mmol/L
Phosphorus	mmol/L
Total bilirubin	µmol/L
Bilirubin, Direct	µmol/L
Bilirubin, Indirect	µmol/L
Aspartate amino transferase (AST)	U/L
Alanine amino transferase (ALT)	U/L
Alkaline phosphatase	U/L
Lactate dehydrogenase (LDH)	U/L
Triglycerides	mmol/L
Serum creatinine	µmol/L
eGFR	mL/min/1.73m²

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

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

Vital signs include the following parameters, which will be presented in this order:

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Pulse Rate (bpm)
- Body Temperature (°C) for pediatric cohort only
- Blood oxygen saturation (%) for pediatric cohort only

The parameters are measured at the following time points:

- Prior to each contrast agent injection (baseline value is measurement prior to the first agent injection)
- Between 30 and 75 minutes after each contrast agent injection
- One day after each contrast injection

ECG data include the following parameters which will be collected and presented only for pediatric cohort:

- Heart rate (bpm)
- Intervals: RR, PR, QRS, QT [corrected QT (QTc) will be calculated according to Fridericia and Bazett methods]
- Global morphology (normal or abnormal ECG)
- findings (if any)

Heart rate, interval and global morphology will be measured in triplicate at the following time points:

- Prior to gadopiclenol injection (baseline value is the last measurement prior to the agent injection),
- Between 30 and 75 minutes after gadopiclenol injection
- One day after gadopiclenol injection.

The 3 measurements of each triplicate of heart rate and intervals will be averaged and considered as one measure for the reporting. The same rule applies in case of missing data. The worst case scenario will be considered for the global morphology. Hence, if at least one replicate is indicated as being abnormal then the global timepoint will be considered as abnormal. The result for the triplicate will be considered as one measure for the reporting.

2.3.5. Medications and procedures

Procedures collected are only those related to an adverse event.
Prior medications / procedures are medications /procedures ended before the first IMP administration.
Concomitant medications / procedures are treatments or procedures on-going at the first IMP administration or administered until end of study. Hence for the adult cohort, a medication / procedure which started before the first IMP administration and ongoing after the second IMP administration is considered as a concomitant medication /procedure for both IMPs.

Medications will be coded using the World Health Organization (WHO) Drug dictionary last version at the time of the database lock.

Procedures related to a reported AE will be coded using the MedDRA dictionary last version at the time of the database lock.

2.4. Pharmacokinetics data

Gadopiclenol pharmacokinetics (PK) in plasma will be assessed for pediatric patients in the PK subgroup.
Following PK parameters will be determined from the population PK model:

- Simulated concentrations at 10-, 20- and 30minutes post injection,
- Area Under the Curve (AUC),
- Elimination half-life,
- Total clearance,
- Volume of distribution.

A separate population PK analysis plan will describe the analyses.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed by Aixial under the supervision of GUERBET AND BRACCO Biostatisticians on the basis of the present document.

A quality control of the statistical analysis will be performed to ensure the reliability of the results.

Thorough description of all parameters reported will be presented separately by group. Summary tabulated results will be provided by group and assessment time, if relevant or they will be replaced by the corresponding individual data listings if too few subjects are concerned.

Tabulations of quantitative parameters will include the following summary statistics: Number of Subjects / 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.

All statistical tests will be performed at the significant threshold of 2.5% one sided.

The SAS Viya 3.5 (SAS Studio 5.2 or higher) will be used for all descriptive summaries and inferential analyses.

3.2. Null and alternative hypothesis

Primary objective (only for adult cohort)

- Non-inferiority margin:

A direct demonstration of the superiority of gadopiclenol images over unenhanced images will be provided in a secondary analysis. Therefore, it is not necessary to define a value for non-inferiority margin to establish that gadopiclenol has efficacy over unenhanced images.
A 10% non-inferiority margin was considered clinically as an unimportant difference and therefore relevant to establish acceptable efficacy relative to gadobutrol. Based on the GUERBET Phase III GDX-44-010 and GDX-44-011 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: μ =-0.35

Alternative hypothesis H_1: μ > -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.

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.

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

Efficacy objective of superiority of Paired vs. pre for pediatric patients

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: μ = 0

Alternative hypothesis H_1: μ > 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 for a blinded reader.

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 (adult cohort only)

The standard deviation on lesion visualization criteria for gadopiclenol is estimated on the basis of the GUERBET Phase III GDX-44-010 and GDX-44-011 clinical trials results on lesion visualization criteria presented in the table below.

GDX-44-010 - *Mean (SD) of the combined unenhanced and gadopiclenol-enhanced imaging.*

Reader	N	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	227	3.91 (0.28)	3.93 (0.28)	3.78 (0.62)
2	231	3.64 (0.60)	3.64 (0.58)	3.57 (0.70)
3	220	3.95 (0.15)	3.97 (0.16)	3.89 (0.38)

GDX-44-011 - *Mean (SD) of the combined unenhanced and gadopiclenol-enhanced imaging.*

Reader	N	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	240	3.82 (0.38)	3.83 (0.37)	3.69 (0.58)
2	223	3.56 (0.69)	3.75 (0.53)	2.88 (1.07)
3	243	3.53 (0.53)	3.74 (0.45)	3.35 (0.58)

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 (many body regions), the expected standard deviation of difference between gadopiclenol and gadobutrol is estimated to 1.5.

For this 2x2 cross-over design, the statistical analysis is based on the observed Student's t-based two-sided 95% confidence interval (95%CI) of the gadopiclenol-gadobutrol difference for each co-primary criteria. An enrollment of 150 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin, assuming 80% power and for each co-primary criteria, the expected difference in mean scores equal to 0 with an expected standard deviation of 1.5.
If one assumes a non-evaluable patient rate (drop-out rate and non-valid primary criterion rate) of about 25%, an enrollment of 200 patients is necessary to meet primary objective for adult patients.

Number of patients for the efficacy objective of superiority of Paired vs. pre for pediatric patients:

Sample size was calculated by considering following results of the 2 phase 3 trials GDX-44-010 and GDX-44-011:
GDX-44-010 - *Mean (SE) of the difference between combined unenhanced and gadobutrol-enhanced imaging vs unenhanced imaging.*

Reader	N	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	227	1.82 (0.03)	2.26 (0.03)	2.77 (0.04)
2	229	1.90 (0.05)	1.77 (0.04)	2.58 (0.05)
3	202	1.36 (0.04)	1.96 (0.05)	2.90 (0.06)

GDX-44-011 - *Mean (SE) of the difference between combined unenhanced and gadobutrol-enhanced imaging vs unenhanced imaging.*

Reader	N	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	251	1.53 (0.04)	1.81 (0.03)	2.64 (0.04)
2	230	0.47 (0.06)	0.53 (0.06)	1.82 (0.07)
3	262	1.71 (0.04)	2.03 (0.04)	2.33 (0.04)

Considering that the effect size will be close to the one of the GDX-44-011 trial and that the heterogeneity will be higher as both, patients referred for CNS and Body regions MRI will be included, the expected difference mean is estimated ranging from 0.5 to 1.5 and the expected SD of the difference is estimated ranging from 1 to 1.5.

Expecting that for each co-primary criteria, the difference in mean scores will be 0.5 (["Paired" – "Pre"] within patient mean of lesion scores) with 1 standard deviation, a sample of 34 children in the gadopiclenol

group will have 80% power when using a single group superiority t-test with a 0.025 one-sided significance level.
The non-evaluable patient rate is expected lower than for the non-inferiority as only one MR evaluation is needed therefore 40 pediatric patients is necessary to show superiority.

3.4. Adjustment for covariates

As no factor has been identified as having a large impact on the primary analysis, no covariates are added in the primary efficacy model.

3.5. Handling of data

3.5.1. Combinations of readers

As different body regions were included in the study, readers with different expertise were needed for the reading of study images. The off-site unpaired evaluation of the blinded images and the global matched-pairs evaluation for overall diagnostic preference and count of lesions were performed by 3 independent blinded radiologists (reader 1, reader 2, reader 3) per body region. The affectation of radiologists to a reader number is set by the central imaging laboratory independently to the sponsors and before any reading therefore, purely at random.

The distribution of the number of independent qualified blinded readers by body region are:
- Three readers for Head and Neck (H&N) and Central Nervous System (CNS)
- Three readers for Thorax (including breast),
- Three readers for Abdomen (including liver, pancreas and kidneys), Pelvis (including uterus, ovary and prostate) and Musculoskeletal (including extremities) (MSK)
- Three readers for Cardiac

Reader A is the pooling of reader 1 for H&N and CNS, reader 1 for Thorax, reader 1 for Abdomen/ Pelvis/ MSK and reader 1 for Cardiac.
Reader B is the pooling of reader 2 for H&N and CNS, reader 2 for Thorax, reader 2 for Abdomen/ Pelvis/ MSK and reader 2 for Cardiac.
Reader C is the pooling of reader 3 for H&N and CNS, reader 3 for Thorax, reader 3 for Abdomen/ Pelvis/ MSK and reader 3 for Cardiac.
All body regions but cardiac are directly identified in the CRF MRI examination page. Cardiac cases should be retrieved by selecting the name “cardiac” in the specify field if “other” is ticked for Thorax patients.

Three secondary analyses are provided with different random combinations to show that the distribution of radiologists into one reader has no impact on the analysis. Combination of radiologists will be named reader D reader E, reader F, for the first analysis, reader G, reader H, reader I for the second analysis, and reader J, reader K, reader L for the third analysis.

3.5.2. Missing dates

3.5.2.1 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.

3.5.2.2 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.

3.5.2.3 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. The number of patients screened in each center will be displayed in a disposition table.

3.8. Multiple comparisons/Multiplicity

No multiplicity adjustment is needed for this trial as only one primary objective should be reached for adult cohort and the pediatric cohort is exploratory.
Furthermore, primary objective (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" of subjects

For the adult cohort, as the primary objective is non-inferiority, the corresponding primary analysis and the sensitivity analyses will be done using the Per Protocol Set then the analyses will be repeated using the Full Analysis Set (FAS).
For the pediatric cohort, all analyses will be done using the FAS.

3.10. Active control studies intended to show equivalence

Not applicable

3.11. Examinations of subgroups

For the adult cohort, primary criteria statistics descriptive will be provided per indication (CNS, Body), per body region subgroups (thorax (including cardiac), pool abdomen and pelvis,), by main demographic parameters (age and sex) and MRI machine field strength. Indication and body region are those on-site and are unique by patient.
Supplementary analyses of the non-inferiority analysis will be conducted using the same linear model with indications, body region subgroups, demographic parameters and MRI machine field as additional factors.

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

The protocol has been amended twice, the first version of Statistical Analysis Plan (SAP) was based on version 3.0 dated 17 February 2023 (first version with recruited patients) and the current version of SAP is based on version 5.0 dated 22 October 2024 (including amendments 1 & 2).

Change between version 3 and version 5 of the protocol:
Minimum number of pediatric patients to be recruited per age group and in PK cohort is alleviated considering that exposure parameters for the uncompleted age groups could be predicted by simulation.
The non-inclusion criterion for patients referred for contrast-enhanced cardiac MRI was modified.

Ten analyzed datasets have been initially defined to deal with all analyses. However, for the adult cohort, the set pooling all randomized patients is not used and so removed. For the pediatric cohort, the dataset that will be used for the PK analysis will be defined in the PKpop plan therefore both PP set and PK set are removed from the SAP.

Improvement in lesion visualization scores at patient-level will not be analyzed. Indeed, this criterion does not convey any additional information on top of what it will be already presented regarding the lesion visualization.

Difference between combined enhanced-unenhanced and unenhanced for lesion visualization criteria will not be analyzed on the PPS in addition on the FAS for adult patients as not needed for the demonstration of superiority.

Sensitivity analyses will not be performed on the FAS in addition on the PPS as sensitivity analyses will present only departures to the main analysis which is presented on PPS.

For the pediatric cohort, the overall disposition will not be presented by age group but only by indication. The same for the number of patients by site that will be presented only overall and no longer by age group.

For the pediatric cohort, the inter-reader variability will be analysed on the FAS instead of the PPS as all efficacy analyses are performed using the FAS.

The location of lesions and the Patient treatment plan will be only listed.

For the adult cohort, the safety parameters (AE, laboratory data and vital signs) will be presented by indication (CNS and Body) instead of body regions.

For both adult and pediatric cohort, no qualitative analysis will be performed for vital signs and ECG.

Changes since the protocol version 5:
The classification Important/non important has been added for all protocol deviations.
Protocol deviations related to the IMP injection were originally presented separately for gadobutrol and gadopiclenol injection. Inversely, they will be presented together; the indication of the type of GBCA used will be only listed.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of subjects

For the adult patient cohort:
The patients' disposition will be presented by sequences (gadopiclenol-gadobutrol / gadobutrol- gadopiclenol) 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 sequences and overall. Randomized patients being defined as patients having a GBCA allocation by IWRS. The same analyses will be repeated by indications (CNS, Body) except reason of screen failure.
Number (%) of patients attending each visit will be presented by sequences and overall.

For the pediatric patient cohort:
Number (%) of patients attending each visit will be presented by age group and overall, in each indication (CNS and body regions) and globally.
The patients' disposition will be presented by age group (CNS and Body confounded) by indication and overall. The reason of screen failure for not administered patients and the reason of premature discontinuation for administered patients will be presented by age group, by indication and overall.

Number of patients by center will be presented by cohort and overall.

5.2. Data Sets Analysed and protocol deviations

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

- The Screened Patients Set adults (SPSa) will include all adult patients having signed the inform consent form
- The Screened Patients Set pediatrics (SPSp) will include all pediatric patients for whom the inform consent form was signed
- The Safety Set adults (SSa) will include all adult patients having received at least one injection of IMP regardless of the quantity
- The Safety Set pediatrics (SSp) will include all pediatric patients having received the injection of IMP regardless of the quantity
- The Full Analysis Set adults (FASa) will include all adult patients who have performed the two enhanced MRI exams
- The Full Analysis Set pediatrics (FASp) will include all pediatric patients who have performed the unenhanced and gadopiclenol-enhanced MRI exam
- The Per-Protocol Set adults (PPSa): will include all patients from the FASa who have no major protocol deviations

	Screened Patient Set (SPS)	Safety Set (SS)	Full Analysis Set (FAS)	Per protocol Set (PPS)
Adults				
Disposition	✓			
Protocol deviations		✓		
Demographics and baseline characteristics		✓		✓
Compliance			✓	

Efficacy evaluation: Primary analysis				✓
Efficacy evaluation: Sensitivity analysis				✓
Efficacy evaluation: Secondary analyses			✓	✓
Safety Evaluation		✓		
Pediatrics				
Disposition	✓			
Protocol deviations		✓		
Demographics and baseline characteristics		✓		
Compliance			✓	
Efficacy Evaluation			✓	
Safety Evaluation		✓		

Protocol deviations

As per ICH E3 guideline, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, with or without impact to the patient/healthy volunteer safety or the efficacy assessments. Protocol deviations are displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. The list of protocol deviations is presented in the table below and can be updated if necessary before breaking the blind. Protocol deviations will be gathered from monitoring files, clinical database and external vendors of off-site data (imaging and PK data)
Protocol deviations will be split in major and non-major deviations (status1) on one hand and in important and non-important deviations (status 2) on the other hand. A major deviation is defined as a deviation having an impact on the primary criterion therefore only applicable for adult cohort. An important deviation is defined as a deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.
A first categorisation is done in this document, then categorisation will be consolidated before breaking the blind, during the statistical data review meeting. The decision will be duly described in the meeting minutes. Deviations will be presented for adult and pediatric cohort separately.

The deviations are listed in the table below:

For pediatric cohort:

Category	**Description**	**Status 1**	**Status 2**
Inclusion criteria not met/ Non inclusion criteria met	Inclusion Criteria not met and patient included.	Non major	Important
	Non-inclusion criteria met and patient included	Non major	Important

Patients not withdrawn as per protocol	Patient becoming pregnant or discovering her pregnancy during trial participation (pregnancy test positive) and not withdrawn	Non major	Important
	Patient with eGFR missing or out of age-adjusted normal values at baseline and not screen failed	Non major	Important
	Patients receiving a contrast agent (for MRI or CT) within 3 days (or 7 days for patients below 1 year old) prior to trial administration or during the trial and not withdrawn	Non major	Important
Missing Data	PK blood sample not performed, or results are missing	Non major	Important
	Vital signs not measured, or results are missing	Non major	Non-important
	Standard 12-lead ECG not performed or results missing	Non major	Non-important
	Biochemistry sample not performed, or results are missing	Non major	Non-important
	Hematology sample not performed, or results are missing	Non major	Non-important
	Age is missing	Non major	Non-important
	Sex is missing	Non major	Non-important
	Height is missing	Non major	Non-important
	Race is missing	Non major	Non-important
	Physical examination not performed	Non major	Non-important
	MRI Machine manufacturer is missing	Non major	Non-important
	MRI machine field strength is missing	Non major	Non-important
	Date or time of injection is missing	Non major	Non-important
IMP deviation	The volume of gadopiclenol actually administered is different from the theoretical one	Non major	Important
	IMP management not appropriate	Non major	Non-important
	Actual gadopiclenol injection rate not adequate for body indication	Non major	Important
	Actual gadopiclenol injection rate not adequate for CNS indication	Non major	Non-important
	Temperature excursion for IMP without impact on product stability	Non major	Important
	Temperature excursion for IMP with impact on product stability	Non major	Important
	Extravasation during IMP administration	Non major	Important
	Saline flush not done after IMP administration	Non major	Non-important
Non respect of study's schedule and procedures	PK blood sample storage conditions not respected	Non major	Non-important
	PK blood sample assessed out of stability period	Non major	Non-important

	Blood samples for PK collected out of the scheduled time windows	Non major	Non-important
	Blood samples for PK collected with no sufficient bio-analytical assessments to calculate reliable estimates of the PK parameters	Non major	Non-important
	Vital signs performed out of the scheduled time windows	Non major	Non-important
	Blood pressure and pulse rate not performed in supine position after a rest for at least 5 minutes	Non major	Non-important
	Blood pressure measured on the arm used for the injection	Non major	Non-important
	Standard 12-lead ECG not performed in supine position after a rest for at least 5 minutes	Non major	Non-important
	ECG measured out of the scheduled time windows	Non major	Non-important
	Blood samples for safety storage conditions not respected	Non major	Non-important
	Blood samples for safety collected out of scheduled time windows	Non major	Non-important
	Time between screening visit and gadopiclenol administration is greater than 14 days	Non major	Non-important
	IWRS recording not appropriate	Non major	Non-important
	PK profile unexpected	Non major	Non-important
Forbidden concomitant medication	Patient having concomitant procedure that may altered gadopiclenol PK parameters	Non major	Non-important
	Patient having received concomitant treatment that may altered gadopiclenol PK parameters	Non major	Non-important
Good Clinical Practice (GCP) deviation	Inform consent form (ICF) management not appropriate	Non major	Important
	Source document management not appropriate	Non major	Non-important
	SAE management not appropriate	Non major	Important

For adult cohort:

Category	Description	Status 1	Status 2
Inclusion criteria not met/ Non inclusion criteria 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	**Major**	Important
	Patients without known or suspected enhancing abnormaliy(ies) and/or lesion(s) in CNS or in at least one body region.	**Major**	Important

Category	Description	Status 1	Status 2
	At least one other inclusion criteria not met	Non major	Non-important
	At least one other non-inclusion criteria met	Non major	Non-important
	eGFR at screening below 30 mL/min/1.73m^2 and contrast agent administered	Non major	Important
	eGFR measurement at screening is missing	Non major	Important
	No pregnancy test done within 1 day before contrast agent administration for female of childbearing potential	Non major	Important
	Result of pregnancy test positive and contrast agent administration performed	Non major	Important
Trial target lesion	Procedure used for detecting the trial target lesion is **not** provided	Non major	Non-important
	Procedure used for detecting the trial target lesion is **not** adequate	Non major	Non-important
	Procedure used for detecting the trial target lesion is not performed within 12 months prior to ICF signature	Non major	Non-important
Imaging	Imaging protocol not respected with major impact on co-primary criteria	**Major**	Important
	Imaging protocol not respected with non-major impact on co-primary criteria	Non major	Non-important
	Deviation to blind charter in regards to data correction	Non major	Non-important
Unblinding	Blind not maintained on site	Non major	Non-important
	Blind not maintained at central reading level	**Major**	Important
Forbidden concomitant medication	Concomitant medication or medical procedure taken between the two MRI significantly impacting lesion size and its enhancement pattern	**Major**	Important
	Concomitant medication or medical procedure taken between the two MRI that may impact the appearance of lesion of the imaged region between the 2 MRI examinations however timing of the exam and/or nature of the lesion exclude potential impact	Non major	Non-important
	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	**Major**	Important
	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	Non major	Important
IMP deviation	Patient does not receive the IMP allocated by randomization	**Major**	Important
	Patient does not receive the kit allocated by IWRS	Non major	Non-important

Category	Description	Status 1	Status 2
	The IMP volume actually administered is different from the theoretical one from 10 to 20%	Non major	Important
	The IMP volume actually administered is different from the theoretical one more than 20% or missing	**Major**	Important
	Actual gadopiclenol injection rate not adequate for body indication	Non major	Important
	Actual gadopiclenol injection rate not adequate for CNS indication	Non major	Non-important
	Temperature excursion for IMP without impact on product stability	Non major	Important
	Temperature excursion for IMP with impact on product stability	Major	Important
	IMP management not appropriate	Non major	Non-important
	Extravasation during IMP administration	**Major**	Important
	Saline flush not done after IMP administration	Non major	Non-important
Missing data	Age is missing	Non major	Non-important
	Sex is missing	Non major	Non-important
	Height is missing	Non major	Non-important
	Race is missing	Non major	Non-important
	Central Laboratory Biochemistry results **not** available	Non major	Non-important
	Central Laboratory Hematology results **not** available	Non major	Non-important
	Vital sign **result** missing	Non major	Non-important
Non respect of study's schedule and procedures	Time between the two MRI procedures is strictly greater than 14 days and less or equal to 21 days	Non major	Non-important
	Time between the two MRI procedures is strictly greater than 21 days	**Major**	Important
	Two different MRI system manufacturers used for both assessments of the same patient	Non major	Non-important
	Two different magnetic field strengths used for both assessments	**Major**	Important
	MRI machine used not qualified	Non major	Non-important
	Body region is different between the two MRs	**Major**	Important
	Physical examination **not** performed	Non major	Non-important
	eGFR method is not accurate	Non major	Non-important
	Time between screening visit and first contrast agent administration is strictly greater than 7 days	Non major	Non-important
	Blood sample for central laboratory assessment is not drawn in the time window allowed by protocol	Non major	Non-important
	Vital sign is not measured in the time window allowed by protocol	Non major	Non-important
	Deviation in IWRS Process	Non major	Non-important
	Clinical protocol procedure not respected	Non major	Non-important
GCP deviation	Deviations related to ICF signature process	Non major	Important
	Source document management not appropriate	Non major	Non-important
	SAE management not appropriate	Non major	Important

Subjects presenting at least one protocol deviation with a status 1 major will be excluded from the PPSa and therefore not taken into account in the analysis supporting the primary objective.

Frequency and percentages of subjects with protocol deviations will be presented breaking down by status 1 (major/non major) and status 2 (important / non important) separately for pediatric and adult cohort. For pediatric cohort, deviations will be tabulated by age group and indication. For adult cohort, deviations will be tabulated by sequences. A listing of all protocol deviations will also be provided in CSR appendix 16.2.3 and major protocol deviations will be flagged.

5.3. Measurements of study drug compliance

For adult patients, compliance with each contrast agent group will be presented using the FASa. 33on pediatric patients, compliance with gadopiclenol will be presented using the FASp by age group and region. 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 for adult patients Cohort), height and BMI. Frequency and percentages will be calculated for sex, contraceptive status and race.
For adult patients' cohort, demographics will be tabulated by sequences and overall using PPSa and by GBCA using the SSa. Same analyses will be repeated by indication using PPSa.
For pediatric cohort, demographics will be tabulated by age group and overall, in each indication (CNS and body regions) and globally using the SSp
Listing of demographic data will be presented in CSR Appendix 16.2.4.

5.4.2. Trial target lesion(s) diagnosis

Trial target lesion(s) 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 sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT.

Time between imaging procedure documenting the trial target lesion(s) diagnosis 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 and listed.
For adult patients, imaging procedure will be tabulated by sequences and overall using PPSa.

For pediatric patients, imaging procedure will be tabulated age group and overall, in each region (CNS and body regions) and globally using the SSp.

Listing of trial target lesion(s) 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 sequences and overall using PPSa for adult patients, and per age group, region and overall using SSp for pediatric patients. Tables will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT.

Listing of all diseases, with a flag for ongoing diseases will be presented in CSR Appendix 16.2.4.

5.4.4. Clinical Laboratory at screening

For adult patients, eGFR results will be tabulated by presenting the number and percentage of patients with eGFR measurement in the following categories:
Below or equal to 30, between 30 excluded and 60 included, between 60 excluded and 90 excluded and more than or equal to 90.
The table will be presented by sequences and overall using the PPSa.
For pediatric patients, eGFR results will be tabulated and the number and percentage of patients with eGFR measurement in the following categories:
Below or equal to 30, between 30 excluded and 60 included, between 60 excluded and 90 excluded and more than or equal to 90
This table will be presented for each age group, cohort and overall using the SSp.

5.4.5. Prior medications

The number and percentage of patients who took prior medications will be summarized according to Anatomical Therapeutic Chemical (ATC) fourth level (ATC 4) by purpose and overall using the FAS. For the pediatric cohort, the table will be presented by age group and region. For the adult cohort, the table will be presented by sequences.
The table will be sorted according to the percentage of patients reporting at least one previous medication from the most to the least frequent globally.

Listing of all medications will be presented in CSR Appendix 16.2.4.

5.4.6. Other baseline characteristics

Previous gadolinium exposure history
Frequency and percentages will be tabulated by contrast agent group and overall for history of previous gadolinium using Safety set. This will be also split by age group and region for the pediatric cohort.
Listing of contrast agent intolerance history will be presented in CSR Appendix 16.2.4.

Physical examination
Physical examination will be only listed.
Listing of physical examination will be presented in CSR Appendix 16.2.4.

Information about MRI examination
Magnetic field strength (1.5 or 3.0 tesla) and regions will be tabulated by contrast agent for adult patients using the PPS and age group for pediatric patients using the FAS.
Listing of MRI examination will be presented in CSR Appendix 16.2.4.

Standard of truth
All analyses will be presented by region for pediatric patients and adult patients separately using the FAS
Number of patients with SOT and final patient diagnosis will be summarized overall.
Time from the SOT evaluation to the first injection, type of sample collection, final patient diagnosis, lesion location and size will be summarized for patients for whom the SOT diagnosis is given by histopathology.
Final patient diagnosis, lesion location and size will be summarized for patients for whom the SOT diagnosis is given by histopathology.
Listing of standard of truth data will be presented in CSR Appendix 16.2.4.

5.5. Efficacy evaluation

5.5.1. Analysis supporting the primary objective

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria in adult patients – at patient level

Each co-primary criterion will be analyzed using a general linear model for each reader independently, modelling the patient's score (average of up to 10 matched lesions scores for a patient) 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 PPS. 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.

5.5.2. Sensitivity analyses

The imputation is done in the way to maximize the difference between gadopiclenol and gadobutrol to show the robustness of the non-inferiority.

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria on lesions detected by gadobutrol – at patient level

Same analysis as the primary analysis will be conducted. All lesions including matching and those detected only by gadobutrol within a reader will be considered for this analysis. Score for lesions not seen with gadopiclenol will be imputed to the worst score equal to 1. Lesions after imputation will be included for the average of patient level score. Therefore, there will not be missing data in the model.

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria on all lesions with imputation- at patient level

Same analysis as the primary analysis will be conducted. All lesions including matching and non-matching within a reader between gadopiclenol and gadobutrol will be considered for this analysis. Score for non-matching lesions will be imputed to the worst score equal to 1. All lesions after imputation will be included for the average of patient level score. Therefore, there will not be missing data in the model.

5.5.3. Supplementary analyses

Main analysis for pediatric patients: superiority of Paired images versus Pre images of gadopiclenol regarding lesion visualization co-primary criteria on matching lesions

Each co-primary criterion will be analyzed using a general linear model for each reader independently, modelling the patient's score (average of up to 10 matched lesions scores for a patient) 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 FASp on matching lesions. Results will be presented per off-site reader.

Superiority of Paired images versus Pre images of gadopiclenol regarding lesion visualization on all lesions with imputation in pediatric patients – at patient level

Same analysis method as above will be carried out. All lesions including matching and non-matching will be considered for this analysis. Score for non-matching lesions will be imputed to the score of the lesion spotted with the other modality ("pre" or "paired"). For example, if a lesion is seen with gadopiclenol-enhanced MRI but not with unenhanced MRI then its score for "Pre" will be equal to the score rated with "Paired". This imputation is done in the way to minimize the difference between "pre" and "paired to show the robustness of the superiority.

Superiority of Paired images versus Pre images of gadopiclenol regarding lesion visualization on matching lesions in adult patients – at patient level

Each co-primary criterion will be analyzed using a general linear model for each reader independently, modelling the patient's score (average of up to 10 matched lesions scores for a patient) 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; .
```

The Student's t-based 95% CI of the difference "Paired" –"Pre" will be constructed for each of 3 co-primary criteria using the PPS. If the lower bound of this confidence interval is above 0 for at least 2 out of 3 readers (same as those for non-inferiority) and for the 3 co-primary criteria, then direct demonstration of the superiority of gadopiclenol images over unenhanced images will be provided and therefore establish that gadopiclenol has efficacy over unenhanced images.

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

Superiority of Paired images versus Pre images of gadopiclenol regarding lesion visualization on all lesions with imputation in adult patients

Same analysis method as above will be carried out. All lesions including matching and non-matching will be considered for this analysis. Score for non-matching lesions will be imputed to the score of the lesion spotted with the other modality ("pre" or "paired"). For example, if a lesion is seen with gadopiclenol-enhanced MRI

but not with unenhanced MRI then its score for "Pre" will be equal to the score rated with "Paired". This imputation is done in the way to minimize the difference between "pre" and "paired to show the robustness of the superiority.

Superiority of Paired images versus Pre images of gadobutrol MR examination regarding lesion visualization on matching lesions in adult patients (assay sensitivity)
Same analysis as above will be carried out. Only matching lesion will be considered for this analysis.

Supportive analyses of the non-inferiority analyses
The analysis supporting the primary objective will be repeated using the FAS and with three different combinations of readers using the PPS.

Descriptive statistics
Descriptive statistics will be presented for Pre and Paired assessment of both GBCA using PPS for matching lesions and using the FAS for all lesions without imputation.

Examinations of subgroups
Analysis with matching lesions only will be conducted using the same linear model as described above for non-inferiority analyses with subgroups as additional factors.

The model syntax will be as follows:

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

Indication
Indication is brain and spine (named as CNS) on one hand or other body regions (named as body) on the other hand.

For each indication, 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. Results will be presented per off-site reader using the PPSa.

Body region
Body regions are subgroups of the body indications: Thorax (including cardiac) on one hand, Abdomen, Pelvis pooled together on the other hand. Head and Neck and Musculoskeletal system will not be presented.

The robustness of GBCA effect across different body regions will be discussed with following information using the PPSa:

- Descriptive summary statistics for each body region
- 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.

Demographics parameters and magnetic field
Demographic parameters are categorized age and sex.

The robustness of GBCA effect across different parameters will be discussed with following information using the PPSa:

- Descriptive summary statistics for each parameter
- Effect estimations for each parameter with the associated 95% two-sided CI. Overlapping of all parameter CI estimates with the confidence interval for the overall effect will be checked.
- Graphical visualization of the parameters with a Forest plot for parameter of the LS Means difference.

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 using paired images from gadopiclenol and gadobutrol.

Intra-Class Correlation (ICC) coefficients will be assessed as described by Shrout and Fleiss (1979) and McGraw and Wong (1996) only on matching lesion for adult patients using the PPS.

Hence, a two-way random effects ANOVA model with absolute agreement and single reader/measurement (one observation by patient) will be performed for each GBCA separately. The ICC is computed, following the ICC(2,1) in Shrout and Fleiss notation or ICC(A,1) in McGraw and Wong notation, according to the following formulae:

$$\frac{MS_R - MS_E}{MS_R + (k-1)MS_E + \frac{k}{n}(MS_C - MS_E)}$$

Where: MS – mean square; MS_R – between readings mean square (within patient); MS_C – between measurements mean square (between patients); MS_E – residual mean square; n – number of patients; k – number of raters or measurements.

SAS® procedure used for the analyses will be the following for each off-site reader and by GBCA:

```
*title2 'Intraclass Correlations for Intra-Rater Reliability';
proc glm data=&data outstat=_stats_
  class subject reading;
  model var = subject reading;
  run;
data out;
  retain msw msb wms ems edf bms bdf jms jdf k;
  set _stats_;
  if upcase(_type_)='SS1' then delete;
  if upcase(_source_)='ERROR' then do;
     ems=ss/df;
     edf=df;
  end;
  if upcase(_source_)="%upcase(usubjid)" then do;
     bms=ss/df;
     msb=bms;
     bdf=df;
  end;
  if upcase(_source_)="%upcase(reading)" then do;
     jms=ss/df;
     jdf=df;
     k=df+1;
  end;
```

```
  if last._name_ then do;
    msw=((ems*edf)+(jms*jdf))/(edf+jdf);
    wms=msw;
    n=bdf+1;
    sfrandom=(bms-ems)/ ((bms)+((k-1)*ems)+((k*(jms-ems))/n)); * ICC(2,1);
    output;
  end;
run;
```

For pediatric patients re-read images will be listed along with corresponding first read images.

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 and using paired images.

A two-way random effects ANOVA model with consistency and multiple readers/measurements will be performed by GBCA only on matching lesion for adults patients and overall for pediatric patients using the PPSa and FASp respectively.
The ICC is computed, following the ICC(3,3) in Shrout and Fleiss notation or ICC(C,3) in McGraw and Wong notation, according to the following formulae:

$$\frac{MS_R - MS_E}{MS_R}$$

Where MS – mean square; MSR - between readers mean square; MSE - residual mean square.

SAS® procedure used for the analyses will be the following for each GBCA:

```
*title2 'Intraclass Correlations for Inter-Rater Reliability';
proc glm data=data outstat=_stats_
  class usubjid rater;
  model var = usubjid rater;
  run;

data out;
  retain msw msb wms ems edf bms bdf jms jdf k;
  set _stats_;
  if upcase(_type_)='SS1' then delete;
  if upcase(_source_)='ERROR' then do;
     ems=ss/df;
     edf=df;
  end;
  if upcase(_source_)="%upcase(usubjid)" then do;
     bms=ss/df;
     msb=bms;
     bdf=df;
  end;
  if last._name_ then do;
    sffixedk=(bms-ems)/bms;                 * ICC(3,3) with no interaction assumption;
    output;
  end;
run;
```

Check of normality assessment

Normal Probability Plot where the ranked residual values are plotted against the normal scores will be displayed for the analysis supporting the primary objective.

5.5.4. Analyses of the secondary criteria

Body region which was scanned (collected as anatomy) according to off-site reader will be only listed

Lesion visualization criteria at lesion level
Each lesion visualization criterion will be analyzed using a general linear model for each reader independently, modelling the lesion's result as a function of the size of the lesion as per the paired gadopiclenol image (=<1 cm, >1cm and =<2 cm, 2 cm) and respectively the contrast agent group (GBCA: gadopiclenol and gadobutrol) for adult patients and as a function of MRI modality (PRE an PAIRED) for pediatrics patients with repeated measures on the lesion due to the pairing of contrast agents / MRI modalities in lesions.

For adult patients, the parameters of the general linear model will be estimated as for the analysis supporting the primary objective but considering lesions as subject. For pediatric patients, they will be estimated as for the main analysis but considering lesions as subject.

The Student's t-based 95% confidence intervals of the difference between gadopiclenol and gadobutrol for adult patients and between PAIRED and PRE for pediatric patients will be constructed for each of 3 criteria using the PPS for adult patients and FAS for pediatric patients on matching lesions.

Technical adequacy of images
The quality of images will be assessed by off-site readers and on-site radiologists. Technical adequacy for diagnosis will be tabulated by contrast agent groups and readers for adult patients and by MRI modalities (pre and paired) and readers for pediatric patients using FAS. Off-site and on-site reader's outcomes will be separately analyzed. Technical adequacy assessed on unenhanced MRI for adult patients and non-diagnostic reasons for both cohorts will be only listed.

Lesion detection
By reader, for patients with all lesions tracked (less than or equal to 10 lesions), the number of lesions detected per patients will be cross tabulated between gadopiclenol and gadobutrol using FASa.

By reader, for patients with all lesions tracked (less than or equal to 10 lesions), number of common lesions detected on both MRIs will be cross tabulated with number of lesions detected on gadobutrol MRI only overall using FASa.

Number of lesions
The number of lesions by patient will be assessed by off-site readers and on-site radiologists and will be tabulated (in class: No lesion / 1 lesion / 2 lesions / 3 lesions / between 4 and 10 lesions / More than 10 lesions) by contrast agent groups and readers using FASa for off-site data of adult patients, by contrast agent groups and MRI modalities (pre and paired) using FASa for on-site data of adult patients and by MRI modalities (pre and paired) using FASp for pediatric patients. Off-site and on-site reader's outcomes will be separately analyzed.

Size of lesions
The size (largest diameter) of the 10 largest and most enhancing lesions will be summarized by body regions; by contrast agent groups for adult patients and MRI modalities (pre and paired) for pediatric patients. Off-site and on-site reader's outcomes will be separately analyzed.
Analysis will display the number and percentage of lesions by category (=<1 cm, >1cm and =<2 cm, 2 cm).
Size of lesion assessed on unenhanced MRI for adult patients will be only listed.

Location
The localization of the 10 largest and most enhancing lesions will be listed.

Diagnostic confidence
For each category of tumor (Non-tumor, Benign tumor and Malignant tumor), the level of diagnostic confidence will be summarized qualitatively by contrast agent groups for adult patient; by MRI modalities (pre and paired) for pediatric patient. Off-site and on-site reader's outcomes will be separately analyzed.
Diagnosis confidence assessed on unenhanced MRI for adult patients and diagnosis for all patients will be listed.

Impact of contrast-enhanced MRI on patient treatment plan
The impact on patient treatment plan will be listed.

Percentage Enhancement of lesions (E%)
E% is calculated from the Signal Intensity (SI) measurement of maximum 3 most representative lesions by the 3 global matched pairs off-site readers for adult patients in the FAS. The mean of E% will be calculated by patient using up to 3 lesions that are assessed.
For each reader, E% will be tabulated by contrast agent groups. 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; .
```

The analysis will be repeated by indication (CNS and Body) for adult patients.

Lesion to Background Ratio (LBR)
LBR is calculated from the SI measurement of maximum 3 most representative lesions by the 3 independent global matched pairs off-site readers for adult patients in the FAS. Then, the mean of LBR will be calculated by patient using up to 3 lesions that they are assessed.
For each reader, LBR will be tabulated by contrast agent groups on pre contrast and paired images.
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;
```

The analysis will be repeated by indication (CNS and Body).

Contrast to Noise Ratio (CNR)

CNR is calculated from the SI measurement of maximum 3 most representative lesions by the 3 independent global matched pairs off-site readers for adult patients in the FAS and in the CNS indication. Then, the mean of CNR will be calculated by patient using up to 3 lesions that they are assessed.

For each reader, CNR will be tabulated using FAS by contrast agent groups on pre contrast and paired images. 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 global matched pairs reader (only for adult patients), 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.

The analysis will be repeated by indication (CNS and Body).

Lesion categorization with enhanced images compared to standard of truth

Gadopiclenol results

For all adult patients having a standard of truth (SOT), Gadopiclenol imaging diagnosis (Tumor or Not-tumor) will be presented for all 3 off-site readers, displaying number and frequency for each SOT group Tumor or Not-tumor using the FAS according to the table below.

		Standard of Truth		
		Tumor	Not-tumor	
Gadopiclenol imaging expert	Tumor	True positive *n1*	False positive *n2*	Total *n1+n2*
	Not-tumor	False negative *n3*	True negative *n4*	Total *n3+n4*
		Total *n1 + n3*	Total *n2+n4*	All total *N+*

The following parameters will be calculated:

- **Sensitivity**: the number of true tumor lesions divided by all lesions considered as tumor according to SOT (*n1 / n1+n3*)
- **Specificity**: the number of true not-tumor lesions divided by all lesions considered as not tumor by SOT (*n4 / n2+n4*)
- **Accuracy**: the number of true tumor lesions and true not-tumor lesions over all lesions (*n1+n4 /N+)*
- **Positive predictive value**: the number of true tumor lesions /all tumor lesions according to Gadopiclenol imaging (*n1 / n1+n2*)
- **Negative predictive value**: the number of true not-tumor lesions /all not tumor lesions according to Gadopiclenol imaging (*n4 / n3+n4)*

For all adult patients having a tumor lesion as per SOT, Gadopiclenol imaging diagnosis (Benign or Malignant) will be presented for all 3 off-site readers, displaying number and frequency for each SOT group Benign or Malignant using the FAS according to the table below.

		Standard of Truth		
		Malignant	Benign	
Gadopiclenol imaging expert	Malignant	True positive *n1*	False positive *n2*	Total *n1+n2*
	Benign	False negative *n3*	True negative *n4*	Total *n3+n4*
		Total *n1 + n3*	Total *n2+n4*	All total *N+*

The following parameters will be calculated:

- **Sensitivity**: the number of lesions showing true malignancy divided by all lesions considered malignant according to SOT (*n1 / n1+n3*)
- **Specificity**: the number of lesions showing true benign divided by all lesions considered as Benign as SOT (*n4 / n2+n4*)
- **Accuracy**: the number of lesions showing true malignancy and true benign over all lesions (*n1+n4 /N+)*
- **Positive predictive value**: the number of lesions showing true malignancy /all lesions showing malignancy according to Gadopiclenol imaging (*n1 / n1+n2*)
- **Negative predictive value**: the number of lesions showing true benign /all lesions not showing malignancy according to Gadopiclenol imaging (*n4 / n3+n4)*

<u>Comparison between Gadopiclenol and Gadobutrol</u>

Two comparisons will be done.

For all adult patients having a SOT:

The sensitivity of the two GBCAs will be compared using a logistic regression modelling the probability that a lesion is a tumor as a function of the GBCA administered for all 3 off-site readers.
The specificity of the two GBCAs will be compared using a logistic regression modelling the probability that a lesion is not a tumor as a function of the GBCA administered for all 3 off-site readers.

For all adult patients having a tumor lesion as per SOT.
The sensitivity of the two GBCAs will be compared using a logistic regression modelling the probability that a lesion is "malignant" as a function of the GBCA administered for all 3 off-site readers.
The specificity of the two GBCAs will be compared using a logistic regression modelling the probability that a lesion is "benign" as a function of the GBCA administered for all 3 off-site readers.

Mc Nemar's test will be carried out to compare the two GBCAs for all 3 off-site readers and for both specificity and sensitivity.

The parameters of the generalized estimating equation (GEE) will be estimated using the SAS® procedure Glimmix. The procedure will be the following for each off-site reader on the FASa:

```
proc glimmix data = &data.;
  class patient GBCA;
    model &var. = GBCA / dist = bin link = id;
    random _residual_ / subject = patient;
    lsmeans GBCA / pdiff = controlu('Gadobutrol') tdiff cl alpha = 0.025;
    lsmeans GBCA;
    estimate "Gadopiclenol - Gadobutrol" GBCA 1 -1 /cl;
run;
```

Listing of SOT results for both adult and pediatric patients will be presented alongside corresponding results of off-site imaging readers.
Listing of all efficacy data will be presented in CSR appendix 16.2.6.

5.6. Safety Evaluation

The safety evaluation will be presented using the Safety Set. For adult patients, summary tables will be presented by GBCA and for pediatric patients, by age group except otherwise specified. Adult and pediatric cohorts will be presented separately.

5.6.1. Extent of Exposure

For adult patients:
Time when AE is considered as Treatment Emergent will be presented by GBCA:

- Time between 1st and 2nd IMP administrations for patients in the sequence 1 combined with Time between 2nd IMP administration and patient's last contact for patients in the sequence 2 for one GBCA.
- Time between 1st and 2nd IMP administrations for patients in the sequence 2 combined with Time between 2nd IMP administration and patient's last contact for patients in the sequence 1 for the other GBCA.

For pediatric patients:
Period when AEs are considered as Treatment Emergent will be presented by GBCA:

- Time between IMP administrations and last contact.

Volume actually administered, actual injection rate (as quantitative variable and as qualitative dichotomized as follow: <2 mL/s, between 2 and 3 mL/s including, >3mL/s), location of injection site, mode of injection, injection of saline flush and occurrence of an overdose will be tabulated.

Listing of exposure will be presented in CSR appendix 16.2.5.

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

- All AEs.
- Serious AEs (SAEs) (variable "serious" classified as yes or missing) and by Seriousness criteria (patients with AEs having different seriousness criteria will be counted in each category of seriousness criterion).
- AEs of special interest (AESIs) (preferred term is Nephrogenic systemic fibrosis).
- AEs with causal relationship to a study 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 study 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 for Treatment Emergent AEs (TEAEs) by contrast agent groups for adults patient. The terms "NTEAE" will be replaced by "TEAE". The following variables will be presented in addition:

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

Same analyses will be repeated by indications.

The number and percentage of patients with at least one TEAE and the number of TEAE will be presented 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 indications for adult patients.

TEAEs with Causal Relationship to the IMP

The number and percentage of patients with at least one TEAE with causal relationship to the IMP and the number of corresponding TEAE will be presented according to Primary SOC and PT. AEs with causal relationship to the IMP are those described by the investigator with causal relationship to the IMP "related" or missing.
Same analyses will be repeated by indications for adult patients.

TEAEs with Causal Relationship to a Study Procedure

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

Deaths, serious adverse events and other significant adverse events

Deaths, AESI and SAEs will be listed (if any). These listings will be sorted by patient number, date/time of onset, end date, Primary SOC, PT, and description.

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

5.6.3. Clinical laboratory evaluation

Hematology and biochemistry parameters will be described as quantitative variables and qualitative variables in SI units. Original units will be only listed.

Quantitative analyses will be done by tabulating raw data (predose and each of the postdose) and change from baseline.

Qualitative analyses will be done via:

- Comparison of laboratory data to their reference ranges
- Shift tables presenting relative change from baseline in eGFR, creatinine and blood urea nitrogen in classes ($\leq$ -50%, > -50% and $\leq$ -25%, > -25% and $\leq$ -15%, > -15% and < 0%, $\geq$ 0% and < 15%, $\geq$ 15% and < 25%, $\geq$ 25% and < 50% and $\geq$ 50 %) will be displayed.

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).

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

5.6.4.1 Vital signs

Vital signs parameters will be presented at each time point.
Quantitative analyses will be done by tabulating raw data (predose and each of the postdose) and changes in vital signs parameter from baseline.

Same analyses will be repeated by indications for adult patients.

5.6.4.2 ECG

Raw data (predose and each of the postdose) and changes from baseline for heart rate, durations, intervals, and global morphology will be tabulated at each time point and listed.
Findings will be only listed

Listings of ECG and vital signs will be provided in CSR appendix 16.2.9.

5.6.5. Concomitant medications and procedures

The number and percentage of patients who took concomitant medications will be summarized according to ATC fourth level (ATC 4) by purpose.
The table will be sorted according to the percentage of patients reporting at least one concomitant medication from the most to the least frequent globally.

The number and percentage of patients with at least one procedure related to a TEAE and the number of corresponding procedures will be presented according to primary SOC and PT.

Listing of all medications and procedures will be presented in CSR Appendix 16.2.4.

6. LIST OF TABLES, FIGURES AND LISTINGS

6.1. Contents of clinical study report section 14

6.1.1. Demographic data

6.1.1.1 Disposition of Subjects

Table 14.1.1.1: Patient Overall Disposition – Screened Patients Set adults
Table 14.1.1.2 : Overall Disposition by indication – Screened Patients Set adults
Table 14.1.1.3 : Reason for Screening Failure – Screened Patients Set Adults
Table 14.1.1.4 : Reason for Premature Discontinuation – All Randomized Adult Patients
Table 14.1.1.5 : Reason for Premature Discontinuation by indication – All Randomized Adult Patients
Table 14.1.1.6: Patient Disposition by Visit - Screened Patients Set Adults
Table 14.1.1.7 : Patient Overall Disposition – Screened Patients Set Pediatrics
Table 14.1.1.8 : Reasons for Screening Failure – Screened Patients Set Pediatrics
Table 14.1.1.9 : Reasons for Premature Discontinuation – Screened Patients Set Pediatrics – Administered Patients
Table 14.1.1.10: Patient Disposition by Visit - Screened Patients Set Pediatrics
Table 14.1.1.11 : Number of Patients by Center - Screened Patients Set Adults and Pediatrics

6.1.1.2 Protocol Deviations

Table 14.1.2.1 : Major Protocol Deviations - All Randomized Adult Patients
Table 14.1.2.2 : Non Major Protocol Deviations - All Randomized Adult Patients
Table 14.1.2.3 : Important Protocol Deviations - All Randomized Adult Patients
Table 14.1.2.4 : Non Important Protocol Deviations - All Randomized Adult Patients
Table 14.1.2.5 : Important Protocol Deviations – All Pediatric Administered Patients
Table 14.1.2.6 : Non Important Protocol Deviations – All Administered Pediatric Patients

6.1.1.3 Data Sets Analysed

Table 14.1.3.1 : Analysis Data Sets: Full Analysis and Per Protocol Sets - Screened Patients Set Adults
Table 14.1.3.2 : Analysis Data Sets: Safety Set - Screened Patients Set Adults
Table 14.1.3.3 : Analysis Data Sets – Screened Patients Set Pediatric

6.1.1.4 Demographics and Baseline Characteristics

Table 14.1.4.1 : Demographic Data –PPSa
Table 14.1.4.2 : Demographic Data by Indication – PPSa
Table 14.1.4.3 : Demographic Data– SSa
Table 14.1.4.4 : Demographic Data – SSp
Table 14.1.4.5 : Imaging Procedure Documenting the Trial Target Lesion(s) Diagnosis – PPSa
Table 14.1.4.6 : Imaging Procedure Documenting the Trial Target Lesion(s) Diagnosis – SSp
Table 14.1.4.7 : Medical History According to Primary System Organ Class and Preferred Term – PPSa
Table 14.1.4.8 : Concomitant Disease According to Primary System Organ Class and Preferred Term – PPSa
Table 14.1.4.9 : Medical History and Concomitant Disease According to Primary System Organ Class and Preferred Term – SSp
Table 14.1.4.10 : Patient's History of Previous Gadolinium Exposure – Safety Set Adult
Table 14.1.4.11 : Patient's History of Previous Gadolinium Exposure – Safety Set Pediatric
Table 14.1.4.12 : eGFR at screening – PPSa
Table 14.1.4.13 : eGFR at screening – SSp
Table 14.1.4.14 : Prior Medications According to ATC first and fourth levels – PPSa
Table 14.1.4.15 : Prior Medications According to ATC first and fourth levels – SSp

6.1.1.5 MRI Examination

Table 14.1.5.1 : MRI Examination – PPSa
Table 14.1.5.2 : MRI Examination – FASp

6.1.1.6 Standard of Truth

Table 14.1.6.1 : Standard of Truth – FASa
Table 14.1.6.2 : Standard of Truth – FASp

6.1.1.7 Compliance with Trial product

Table 14.1.7.1 : Compliance with Trial Product – FASa

Table 14.1.7.2 : Compliance with Trial Product – FASp

6.1.2. Primary Efficacy Co-primary Criteria

6.1.2.1 Analysis supporting the primary objective
Table 14.2.1.1 : Co-primary criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions - Gadopiclenol vs gadobutrol - Mixed Models – PPSa

6.1.2.2 Sensitivity analyses
Table 14.2.2.1 : Co-primary criteria - Off-Site Readings – Analysis at Patient level based on lesions detected by gadobutrol alone - Gadopiclenol vs gadobutrol - Mixed Models - PPSa
Table 14.2.2.2 : Co-primary criteria - Off-Site Readings – All lesions with imputation – Analysis at Patient level based on All lesions - Gadopiclenol vs gadobutrol - Mixed Models - PPSa

6.1.2.3 Supplementary analyses
Table 14.2.3.1 : Lesion visualization criteria - Off-Site Readings – Matching lesions - Analysis at Patient level based on Mixed Models– Paired vs. Pre - FASp
Table 14.2.3.2 : Lesion visualization criteria - Off-Site Readings – All lesions with imputation - Analysis at Patient level based on Mixed Models - Paired vs. Pre - FASp
Table 14.2.3.3 : Lesion visualization criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions - MRI with Gadopiclenol – PAIRED vs PRE - Mixed Model - FASa
Table 14.2.3.4 : Lesion visualization criteria - Off-Site Readings- Analysis at Patient level based on all lesions with imputation - FASa – MRI with Gadopiclenol – PAIRED vs PRE - Mixed Model
Table 14.2.3.5 : Lesion visualization criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions - MRI with Gadobutrol – PAIRED vs PRE - Mixed Model - FASa
Table 14.2.3.6 : Co-primary criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions - Gadopiclenol vs gadobutrol - Mixed Models - FASa
Table 14.2.3.7 : Lesion visualization criteria - Off-Site Readings– Analysis at Patient level based on Matching lesions with first additional reader combination - Gadopiclenol vs gadobutrol - Mixed Models - PPSa
Table 14.2.3.8 : Lesion visualization criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions with second additional reader combination - Gadopiclenol vs gadobutrol - Mixed Models - PPSa
Table 14.2.3.9 : Lesion visualization criteria - Off-Site Readings – Analysis at Patient level based on Matching lesions with third additional reader combination - Gadopiclenol vs gadobutrol - Mixed Models - PPSa

6.1.3. Secondary efficacy criteria

Table 14.2.4.27 : Percentage of enhancement - Off-Site Readings - Gadopiclenol vs Gadobutrol - Descriptive Statistics by indication – FASa
Table 14.2.4.28 : Percentage of enhancement - Off-Site Readings - Gadopiclenol vs Gadobutrol by indication – Mixed Model – FASa
Table 14.2.4.29 : Lesion to Background Ratio - Off-Site Readings - Descriptive Statistics- Gadopiclenol vs Gadobutrol – FASa
Table 14.2.4.30 : Lesion to Background Ratio - Off-Site Readings - Gadopiclenol vs Gadobutrol – Mixed Model – FASa
Table 14.2.4.31 : Lesion to Background Ratio - Off-Site Readings - Descriptive Statistics by indication- Gadopiclenol vs Gadobutrol – FASa
Table 14.2.4.32 : Lesion to Background Ratio - Off-Site Readings by indication - Gadopiclenol vs Gadobutrol – Mixed Model – FASa
Table 14.2.4.33 : Contrast to Noise Ratio - Off-Site Readings - Descriptive Statistics- Gadopiclenol vs Gadobutrol – FASa - Patients in CNS region
Table 14.2.4.34 : Contrast to Noise Ratio - Off-Site Readings - Gadopiclenol vs Gadobutrol – Mixed Model – FASa - Patients in CNS region
Table 14.2.4.35 : Overall Diagnostic Preference and Reason by indication- Off-Site Readings –FASa
Table 14.2.4.36 : MRI Diagnostic Performance, Detection of Tumor*, Patient Level - Off-Site Readings –FASa
Table 14.2.4.37 : MRI Diagnostic Performance, Detection of Malignancies*, Patient Level - Off-Site Readings –FASa (N=xxx) – Patients with Tumor as per Standard of Truth

6.1.4. Safety data

6.1.4.1 Extent of exposure
Table 14.3.1.1 : Summary of Trial Participation Duration – Safety Set Adult
Table 14.3.1.2 : Trial Contrast Agent Administration Modalities – Safety Set Adult
Table 14.3.1.3 : Summary of Trial Participation Duration – Safety Set Pediatric
Table 14.3.1.4 : Trial Contrast Agent Administration Modalities – Safety Set Pediatric

6.1.4.2 Adverse events
Table 14.3.2.1 : Non-Treatment Emergent Adverse Events – Overview – Screened Patients Set Adult
Table 14.3.2.2 : Non-Treatment Emergent Adverse Events –Overview – Screened Patients Set Pediatric
Table 14.3.2.3 : Treatment Emergent Adverse Events – Overview – Safety Set Adult
Table 14.3.2.4 : Treatment Emergent Adverse Events –Overview by Indication (CNS and Body) – Safety Set Adult
Table 14.3.2.5 : Treatment Emergent Adverse Events – Overview – Safety Set Pediatric
Table 14.3.2.6 : Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Set Adult
Table 14.3.2.7 : Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term by Indication (CNS and Body) – Safety Set Adult
Table 14.3.2.8 : Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Set Pediatric
Table 14.3.2.9 : Treatment Emergent Adverse Events with Causal Relationship to IMP by Primary System Organ Class and Preferred Term – Safety Set Adult

6.1.4.3 Laboratory data

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

Table 14.3.4.6 : Concomitant Medications According to ATC first and fourth levels – Safety Set Pediatric
Table 14.3.4.7 : Concomitant procedures by Primary System Organ Class and Preferred Term – Safety Set Adult
Table 14.3.4.8 : Concomitant procedures by Primary System Organ Class and Preferred Term – Safety Set Pediatric

6.2. Contents of clinical study report section 16.2

6.2.1. Disposition of Subjects (Section 16.2.1 of ICH Report)

Listing 16.2.1.1 Final Status - All Adult Patients
Listing 16.2.1.2 Trial Premature Discontinuation for Patients not Completing the Trial - All Adult Patients
Listing 16.2.1.3 Visit Dates - All Adult Patients
Listing 16.2.1.4 Final Status - All Pediatric Patients
Listing 16.2.1.5 Trial Premature Discontinuation for Patients not Completing the Trial - All Pediatric Patients

6.2.2. Protocol Deviations (Section 16.2.2 of ICH Report)

Listing 16.2.2.1 Protocol Deviations - All Randomized Adult patients
Listing 16.2.2.2 Protocol Deviations - All Administered Pediatric Patients

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

Listing 16.2.3.1 Analysis Data Sets - All Adult Patients
Listing 16.2.3.2 Analysis Data Sets – All Pediatric Patients

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

Listing 16.2.4.1 Demographics - SPSa
Listing 16.2.4.2 History of Previous GBCA Exposure - SPSa
Listing 16.2.4.3 Medical History - SPSa
Listing 16.2.4.4 Target lesion Diagnosis - SPSa

Listing 16.2.4.5 Physical Examination - SPSa
Listing 16.2.4.6 Prior and Concomitant Medications - SPSa
Listing 16.2.4.7 Concomitant Procedures - SPSa
Listing 16.2.4.8 Demographics - SPSp
Listing 16.2.4.9 History of Previous GBCA Exposure - SPSp
Listing 16.2.4.10 Medical History - SPSp
Listing 16.2.4.11 Target lesion Diagnosis - SPSp
Listing 16.2.4.12 Physical Examination - SPSp
Listing 16.2.4.13 Prior and Concomitant Medications - SPSp
Listing 16.2.4.14 Concomitant Procedures - SPSp

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

Listing 16.2.5.1 MRI Examination - SPSa
Listing 16.2.5.2 Compliance Data – SPSa
Listing 16.2.5.3 Trial Contrast Agent Administration Modalities - SPSa

Listing 16.2.5.4 MRI Examination - SPSp
Listing 16.2.5.5 Compliance Data – SPSp
Listing 16.2.5.6 Trial Contrast Agent Administration Modalities - SPSp

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

Listing 16.2.6.1 Technical Adequacy and Presence of Lesions- Off-Site Unpaired Assessments- SPSa
Listing 16.2.6.2 Technical Adequacy and Number of Lesions - On-Site Readings -SPSa
Listing 16.2.6.3 Lesion visualization criteria - Off-Site Unpaired Assessments - SPSa
Listing 16.2.6.4 Lesions: Location and Largest Diameter - Off-Site Unpaired Assessments - SPSa
Listing 16.2.6.5 Lesions: Location and Largest Diameter - On-site Readings - SPSa
Listing 16.2.6.6 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Unpaired Assessments - SPSa
Listing 16.2.6.7 Radiological Diagnosis and Level of Diagnostic Confidence - On-site Unpaired Assessments – SPSa
Listing 16.2.6.8 Patient Diagnosis – Standard of Truth and Off-Site Unpaired Assessments - SPSa

Listing 16.2.6.9 Patient Management Plan - On-Site Global Matched Pairs Assessments - SPSa
Listing 16.2.9.10 Number of Lesions, Visibility and Measurability of Lesions - Off-site global Matched Pairs Assessments - SPSa
Listing 16.2.6.11 Signal Intensity Measurements - Off-Site Global Matched Pairs Assessments – SPSa
Listing 16.2.6.12 Overall Diagnostic Preference and Reason - Off-Site Global Matched Pairs Assessments – SPSa
Listing 16.2.6.13 Impact of Patient Management - Off-Site Global Matched Pairs Assessments - SPSa

Listing 16.2.6.14 Technical Adequacy and Number of Lesions- Off-Site Unpaired Assessments- SPSp
Listing 16.2.6.15 Technical Adequacy and Number of Lesions - On-Site Unpaired Assessments -SPSp
Listing 16.2.6.16 Lesion visualization criteria - Off-Site Unpaired Assessments - SPSp
Listing 16.2.6.17 Lesions: Location and Largest Diameter - Off-Site Unpaired Assessments - SPSp
Listing 16.2.6.18 Lesions: Location and Largest Diameter - On-site Readings - SPSp
Listing 16.2.6.19 Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Unpaired Assessments - SPSp
Listing 16.2.6.20 Radiological Diagnosis and Level of Diagnostic Confidence - On-site Unpaired Assessments – SPSp
Listing 16.2.6.21 Patient Diagnosis – Standard of Truth and Off-Site Unpaired Assessments - SPSp

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 - SPSa
Listing 16.2.7.2 Adverse Events Occurring after the First Injection of Contrast Agent - SPSa

Listing 16.2.7.3 Adverse Events of Not Treated Patients or Occurring Prior to the First Injection of Contrast Agent - SPSa
Listing 16.2.7.4 Adverse Events Occurring after the First Injection of Contrast Agent - SPSa

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

Listing 16.2.8.1 Hematology - SI Units - SPSa
Listing 16.2.8.2 Biochemistry - SI Units - SPSa
Listing 16.2.8.3 Hematology – Unscheduled - SI Units - SPSa
Listing 16.2.8.4 Biochemistry - Unscheduled - SI Units - SPSa
Listing 16.2.8.5 Hematology and Biochemistry – Reason Test Not Done - SPSa

Listing 16.2.8.6 Hematology - SI Units - SPSp

Listing 16.2.8.7 Biochemistry - SI Units - SPSp
Listing 16.2.8.8 Hematology – Unscheduled - SI Units - SPSp
Listing 16.2.8.9 Biochemistry - Unscheduled - SI Units - SPSp
Listing 16.2.8.10 Hematology and Biochemistry – Reason Test Not Done - SPSp

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

Listing 16.2.9.1 Vital Signs - SPSa
Listing 16.2.9.2 Vital Signs – Further measurements - SPSa
Listing 16.2.9.3 Vital Signs Not Done - SPSa

Listing 16.2.9.4 Vital Signs - SPSp
Listing 16.2.9.5 Vital Signs – Further measurements - SPSp
Listing 16.2.9.6 Vital Signs Not Done - SPSp
Listing 16.2.9.7 ECG data - Measurement and Interpretation - SPSp
Listing 16.2.9.8 ECG data - Finding - SPSp

7. REFERENCES

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: Uses in assessing rater reliability, Psychological Bulletin 1979, Vol. 86, No. 2, 420-428.

McGraw, K. O., & Wong, S. P. (1996). Forming inferences about some intraclass correlation coefficients. Psychological Methods

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