Efficacy and safety of gadopiclenol for

Magnetic Resonance Imaging (MRI) in Japanese adults and children

Phase III Clinical Trial

CTN number: NA

NATIONAL COORDINATOR(Article 7, Paragraph 1, Item 11）

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Clinical Trial In-Country Representative

CMIC Co., Ltd., 1-1-1, Shibaura, Minato-ku, Tokyo 105-0023, Japan (“**CMIC**”)

Ref. No.: 4_24_00159

PROTOCOL SYNOPSIS

Trial Title:

Efficacy and safety of gadopiclenol for Magnetic Resonance Imaging (MRI) in Japanese adults and children

Phase III Clinical Trial

Trial Product(s): G03277	**Active Ingredient**: gadopiclenol

Potential Participating countries (Potential Number of sites): Approximately 30 sites in Japan

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 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 (thorax, abdomen, pelvis, musculoskeletal) and per organ (if the 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 0.1mmol/kg BW.

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 of gadopiclenol.

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 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.

Number of Patients

- 200 Japanese patients are to be included in the adult cohort.
- 40 Japanese patients are to be included in the pediatric cohort.
  - Up to 24 patients of the pediatric cohort will be included in PK evaluation.

Trial design and methodology

This national trial conducted in Japan includes 2 different cohorts of patients: adult patients and pediatric patients, with two different designs.

- Prospective, multi-center, randomized, double-blind, controlled and cross-over design for the adult cohort.
- Prospective, multi-center, non-randomized, open-label and single arm design for the pediatric cohort.

Adult cohort

The trial includes a maximum of 5 visits and the record of patient's diagnosis as standard of truth:

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

Adult patients, once informed consent form (ICF) signed, will perform a screening visit (V1) to confirm their eligibility for the study, then will be randomized in a 1:1 ratio to one of 2 series 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.

Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the last MRI examination and other clinical information. (see Figure 1)

An Interactive Web Response System (IWRS) will be used to allocate the Investigational Medicinal Product (IMP) and to calculate the volume of IMP to be administered based on the body weight of the patient. In addition, it will guarantee an appropriate representation of the different regions in ensuring the inclusion of:

- at least 80 patients referred for CNS MRI
- at least 80 patients referred for Body 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 MRI

Pediatric cohort

The inclusions will be divided into 4 age groups: patients from birth to 23 months of age inclusive, patients from 2 to 6 years, patients from 7 to 11 years and patients from 12 to 17 years. The recruitment in the 3 older groups of pediatric patients can be conducted in parallel with adult patients' enrolment. The decision to start the inclusion in the group of patients aged from birth to 23 months will be taken by the Trial Safety Review Board (TSRB) based on safety assessments of the first 50 adult patients and the first 10 children enrolled including at least 3 patients from the young children group (aged from 2 to 6 years), as well as GDX-44-015 study data in non-Japanese pediatric patients aged < 2 years old.

The trial includes a maximum of 3 visits and the record of patient's diagnosis as standard of truth:

- One screening visit (V1) up to 7 days prior to the imaging visit (V2) (V1 can be done on the same day as V2 if all the inclusion/non-inclusion criteria are met).

- One imaging visit (V2): will consist of gadopiclenol injection and MRI procedure.
- PK group:
  Blood sampling for PK group will start after gadopiclenol injection according to defined blood sampling schedule and will take up to 8 hours.
- One safety visit (V3): 1 day after gadopiclenol injection and MRI examination.

Pediatric patients, once informed consent form (ICF) signed by the parent(s) or legal guardian(s) (where applicable), will perform a screening visit (V1) to confirm trial eligibility, then will undergo one MRI examination with gadopiclenol (V2), followed by a safety visit (V3) performed 1 day after the MRI visit.

Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the MRI examination and other clinical information. (see Figure 2).

An IWRS will be used to allocate the IMP to be used and to calculate the volume of IMP to be administered based on the body weight of the patient. In addition, it will guarantee an appropriate representation of the different groups of age and regions in ensuring the inclusion as follows:

- Within each age group from 2 to 17 years, at least:
  - 2 patients referred for CNS MRI,
  - 2 patients referred for Body MRI,
  - Other patients can be referred for CNS or Body MRI.

All Patients

Assessment will be done off site by prospective evaluation of the images in a centralized manner. All images will be sent to a core laboratory, which will prepare the images for evaluation. This evaluation will be performed by 3 independent blinded radiologists per anatomical region. Independent blinded radiologists will be assigned to CNS or any Body regions according to their expertise. Furthermore, to allow exact matching of lesions between imaging modalities between Pre and Paired of each contrast agent and between Paired of both contrast agents for Adults, an independent radiologist (lesion tracker) will perform lesion tracking. In addition, images will be evaluated by the on-site investigators.

Pediatric group – PK profile of gadopiclenol in plasma

Up to 24 patients of the pediatric cohort will be included in PK profile assessment.
The approach implemented for PK analyses allows sparse blood sampling only and is selected to minimize the clinical burden to children. Blood sampling will be performed via indwelling catheters rather than by repeated venipunctures. An optimized flexible design with 3 sampling windows (W) covering the first 8 hours following gadopiclenol injection will be used:

- W1: 5 to 60 min post injection
- W2: 2 to 4 hours post injection
- W3: 6 to 8 hours post injection

A total of 3 blood samples per patient will be taken post-injection for PK analysis, one within each window. Details are provided in the POP PK Analytical Plan.

All cohorts

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

During the trial, the safety of the patients will be monitored and assessed based on the reporting of adverse events (AEs), including vital signs, ECG for pediatric patients and clinical laboratory parameters (blood samples).

Eligibility criteria

Inclusion criteria

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

Inclusion criteria for all patients:

1.All Patient presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in CNS or in at least one body region among head & neck, thorax (e.g. breast), abdomen (e.g. liver, pancreas and kidney), pelvis (e.g. uterus, ovary and prostate) and musculoskeletal (e.g. extremities) based on a previous imaging procedure performed within 12 months prior to ICF signature.

2.All If the patient was treated (either with radiation, surgery, biopsy, or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of remaining enhancing abnormality(ies) and/or lesion(s) based on available clinical information.

3.All Patient able and willing to participate in the trial.

4.All Patient affiliated to national health insurance according to local regulatory requirements.

Inclusion criteria for adult patients:

1.A Female or male adult patient having reached legal majority age of 18 years.

2.A Patient scheduled for a contrast-enhanced MRI examination of CNS or a Body region for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the trial.

3.A Patient having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.

Inclusion criteria for pediatric patients:

1.P Female or male pediatric patient from birth to 17 years.

For patients aged from birth to 27 days, only term newborn infants are eligible.
Patients may not have reached the age of 18 years at the MRI examination.

2.P Patient whose parent(s) or legal guardian (where applicable) having read the information provided his/her/their consent to patient's participation in writing by dating and signing the informed consent prior to any trial related procedure being conducted.

3.P Patient with capacity of understanding who received age- and maturity-appropriate information and provided his/her assent to participate in the trial.

Additional inclusion criterion for pediatric patients participating in PK group:

4.P-PK Patient and his/her parent(s) or legal guardian (where applicable) having read the information and provided his/her consent in writing by dating and signing the Informed Consent form or respectively in the patient assent form their consent to participate in the PK analyses.

Non-Inclusion criteria

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

Non-inclusion criteria for all patients:

1bis All Patient referred for contrast-enhanced cardiac MRI as primary examination (e.g. imaging protocol requiring stress or more than a single injection of gadolinium contrast agent) except for late-enhancement cardiac imaging.

2.All Patient having received any investigational medicinal product within 7 days prior to trial entry or scheduled to receive any investigational treatment during the trial.

3.All Patient presenting with any contraindication to MRI examinations.

4.All Patient having received any contrast agent (for MRI or CT) within 3 days (or 7 days for patients <1 year old) prior to trial product administration or scheduled to receive any contrast agent during the trial or within 24 hours after the last trial product administration (or 7 days after for patients <1 year old).

5.All Patient with anticipated, current, or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate in the trial in the Investigator's opinion.

6.All Female patient of childbearing potential with a positive urine pregnancy test done within 1 day prior to each contrast agent administration and not able / not willing to use highly effective birth-controlled method during the trial duration.

Female must have effective medically approved contraception until the last trial visit, if of childbearing potential or with amenorrhea for less than 12 months or must be surgically sterilized or post-menopausal (> 2 years amenorrhea).

7.All Patient unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the trial.

8.All Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

9.All Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other GBCAs (such as hypersensitivity, post contrast acute kidney injury).

Non-inclusion criteria for adult patients:

1.A Patient with acute disease that may rapidly evolve between the 2 MRI examinations

2.A Patient previously randomized in this trial.

3.A Patient expected/scheduled to have any treatment or medical procedure (e.g., chemotherapy, radiotherapy, biopsy, or surgery etc.) that may impact the aspects of the imaged lesions between the 2 MRI examinations. (Patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included).

4bis.A Patient presenting an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² (based on Japanese coefficient-modified CKD-EPI formula) assessed within 1 week prior to the first contrast agent administration.

Non-inclusion criteria for pediatric patients

1.P Patient with previously attributed IMP number in this trial.

2.P Patient with known long QT syndrome.

3.P Patient presenting an estimated Glomerular Filtration Rate (eGFR) outside age-adjusted normal ranges (based on bedside Schwartz equation) assessed within one week prior to contrast agent administration.

Investigational Medicinal Product Administration

Investigational Medicinal Product (IMP) 1, for adult patients and pediatric patients:

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

Investigational Medicinal Product (IMP) 2, for adult patients only:

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

For both products the recommended rate is approximately 2 mL/second followed by a 0.9% saline flush via manual injection or power injector. The injection rate should be identical for both products and may vary depending on scanned organ/region and age of patients.

Trial duration for patients

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

Trial duration for adult patients:

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

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

Maximum trial duration for collection of data:
53 days, if the screening period lasts 7 days, the second MRI is done 14 days after the first one, and patient's diagnosis as a standard of truth is collected within 30 days after the second MRI.

Trial duration for pediatric patients:

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

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

Maximum trial duration for collection of data:
39 days, if the screening period lasts 7 days, and patient's diagnosis as a standard of truth is collected within 30 days after the MRI.

End of trial:

The trial is considered as completed once all the images collected for all the patients have been reviewed by all independent blinded readers and the standard of truth (if available) have been obtained.

Evaluation Criteria

Primary Criterion – Adult Patients only (off-site read)

Lesion visualization: based on 3 co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) assessed by 3 independent blinded off-site readers.

The evaluation will be performed using a 4-point scale for each co-primary criterion and for up to 10 largest and most enhancing lesions. Lesion visualization will be assessed on paired images (pre+post contrast) with gadopiclenol and with gadobutrol.

For each co-primary criterion, a mean of scores will be calculated as follows:

Mean of scores = (score of the lesion 1 + score of the lesion 2 (if any) … + score of lesion n (if any)) divided by the number of lesions (up to 10 lesions)

Secondary evaluation criteria for adult patients:

- Overall diagnostic preference (off-site read). Preference will be determined between the two MRI examinations performed at V2 and V4 and will be evaluated in a global matched-pairs fashion. Reason for preference will also be recorded.
- Patient management plan (on-site read on global matched pairs).
- Quantitative efficacy criteria (off-site read on global matched pairs).
  Contrast to Noise ratio (CNR) in patients referred for CNS MRI only
  Percentage enhancement (E%) of lesion
  Lesion to Background Ratio (LBR)
  CNR, E% and LBR will be calculated at patient level in averaging the parameter for up to the 3 largest most homogeneously enhancing lesions.

Secondary evaluation criteria for all patients:

Qualitative efficacy criteria

- Available patient's diagnosis as per standard of truth (based on histopathology results if available within 30 days after the last MRI examination and other clinical information).
- Lesion visualization: based on 3 co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) assessed on pre and paired images with gadopiclenol by 3 independent off-site blinded readers (off-site read).
- Technical adequacy of images. Images will be evaluated as technically adequate for diagnosis and assessable or not (on-site and off-site read).
- Number, size and location of lesions detected (on-site and off-site read).
- Diagnostic confidence and patient's diagnosis (on-site and off-site read).

Safety criteria

- Adverse Events (AEs)
- Physical examination at screening
- Vital signs: supine systolic and diastolic blood pressures, pulse rate as well as for pediatric patients' body temperature, blood oxygen saturation
- ECG monitoring for pediatric patients centrally assessed
- Laboratory parameter locally assessed at screening only: serum creatinine and eGFR
- Laboratory parameter assessed centrally for adults and by on-site laboratory for pediatric patients:
- Hematology (Red Blood Cells, White Blood Cells, neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, mean red blood cells volume)

- Biochemistry (sodium, potassium, chloride, Blood Urea Nitrogen/ urea, total protein, calcium, phosphorus, bilirubin (total, direct, indirect), Aspartate Amino Transferase, Alanine Amino Transferase, alkaline phosphatase, Lactate DeHydrogenase, triglycerides, serum creatinine)

PK criteria – PK Group

Gadopiclenol pharmacokinetics in plasma will be assessed in the cohort of patients participating in the PK group for both, by age group and overall, based on following pharmacokinetic parameters determined from the population PK model:

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

Time Point for Data Evaluation

Data will be evaluated as soon as data collection for any of the patient cohorts, either of adult or of pediatric patients, has been completed.

Statistical methods

Primary analysis: non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria in adult patients – at patient level.

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

Secondary analyses

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria in adult patients by region.

The non-inferiority will be tested restricted to the patients in the CNS cohort on the one hand and to the patients in Body cohort on the other hand using the same method and the same margin. Results will be presented per reader.

Evaluation of the difference between paired images and pre images of gadopiclenol MR examination regarding lesion visualization in pediatric patients.

The difference "paired" – "pre" for each of the 3 co-primary criteria will be analyzed using paired t-tests on matching lesions. Results will be presented per reader.

Sample Size 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 non-inferiority margin because 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 results of lesion visualization criteria from the GUERBET global Phase III trials (GDX-44-010, CNS indication, and GDX-44-011, Body indication) the mean score for each of the 3 co-criteria is expected to be equal to 3.5, so the margin is set to 0.35 (10%).

- Sample size hypothesis:

An enrollment of 168 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin, assuming 85% 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 15%, an enrollment of 200 adult patients is necessary to meet the primary objective.

Sample Size for pediatric cohort:

Considering an expected difference in mean scores equal to 0.5 and an expected standard deviation of the difference equal to 1. A sample of 38 children in the gadopiclenol group will have 85% power when using a single group superiority t-test with a 0.025 one-sided significance level.

The non-evaluable patient rate is expected to be lower than for the non-inferiority as only one MR evaluation is needed therefore 40 pediatric patients need to be included to guarantee 38 evaluable patients.

For the PK group, although the sample size is not based on statistical consideration, it is estimated that 6 patients per age group, i.e., 24 patients, in the population of the PK analysis will be sufficient to inform gadopiclenol pharmacokinetics in plasma in Japanese children. In case age groups are not or partially completed, the impact of a reduced sample size on the precision of parameter estimates will not be an issue since the available data will be fitted into a model based on a large sample size and including Japanese and non-Japanese adult participants as well as non-Japanese pediatric participants. A simulation approach based on this established model enriched with available Japanese pediatric data, will be used to simulate the missing patients, if any.

TRIAL FLOW CHARTS

Table 1: Trial flow chart for adult patients

Visit [1]	**V1**	**V2**			**V3**	**V4**			**V5**	**Record patient's diagnosis as standard of truth based on histo-pathology results and other clinical information**
Evaluation/ Procedure	**Screening**	**1st Imaging visit (Baseline [9] Randomisation)**			**Safety follow up Post injection**	**2nd Imaging visit (2 d up to 14 d post V2)**			**Safety follow up Post injection**	
Time Point	**≤7 days**	**Prior to MRI**	**MRI**	**30 to 75 min**	**1 day after V2**	**Prior to MRI**	**MRI**	**30 to 75min**	**1 day after V4**	**≤ 30 days after last MRI examination**
Informed consent signature	X									
Eligibility criteria	X	X								
Demographic data, incl. height	X									
Medical history including disease requiring the trial MRIs	X									
History of previous GBCA exposure	X									
Physical examination [2]	X									
Pregnancy test [3]		X				X				
On-site lab Creatinine + e-GFR evaluation [4]	X									
Clinical laboratory parameters [5]		X			X	X			X	
Vital signs (BP, PR) [6]		X		X	X	X		X	X	
Body weight		X				X				
IMP injection			X				X			
Images acquisition			X				X			
IWRS [7]	X	X				X				
Adverse events (AEs) [8]	X									
Concomitant treatments	X									
Procedures/Therapeutic measures	X									
Record of histopathology results and patient's diagnosis										X

(1) V1 can be performed on the same day as V2.
(2) Physical examination is to be performed by a physician: examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information indicating the global assessment (normal or abnormal (specify)) of the physical examination should be recorded on source documentation
(3) Urine pregnancy test (if applicable) is to be done on site. Results must be available prior to IWRS connection and MRI procedures and must be negative to allow administration of IMP.
(4) Creatinine and eGFR are to be evaluated by on-site laboratory. eGFR will be evaluated using Japanese coefficient-modified CKD-EPI formula. Can be done within one week before IMP administration. Results must be available prior to IWRS connection and MRI procedure and must fulfill Non-inclusion criteria to allow-administration of IMP.
(5) Clinical laboratory parameters will be analyzed by the central laboratory: hematology and biochemistry
(6) Vital signs: BP: Blood Pressure (supine systolic and diastolic), PR: Pulse Rate.
(7) IWRS: at V1 the patient number will be assigned; at V2 and at V4 the IMP number will be assigned; and any patient's screening failure or premature discontinuation will be recorded via IWRS.
(8) AEs occurring during the time of the patient's participation in the trial, must be reported and followed, unless they meet the following definition: the events which occur before the first IMP administration, and which are not serious and not related to the trial procedures may be recorded as medical history upon the investigator's judgement. Procedures/therapeutic measures for AE are also to be reported. See section 9 for further information.
(9) All the assessments performed prior to the first MRI at V2 will be considered as baseline value.

Table 2: Trial flow chart for pediatric patients

Visit [1]	**V1**	**V2**			**V3**	**Record patient's diagnosis as standard of truth based on histo-pathology results and other clinical information**
Evaluation/ procedure	**Screening**	**Imaging visit (Baseline** [9]**)**			**Safety follow up Post injection**	
Time Point	**≤7 days**	**Prior to MRI**	**MRI**	**30 to 75 min**	**1 day after V2**	**≤ 30 days after MRI examination**
Informed consent signature	X					
Eligibility criteria	X	X				
Demographic data, incl. height	X					
Medical history including disease requiring the trial MRI	X					
Contrast agents intolerance history	X					
Physical examination [2]	X					
Pregnancy test [3]		X				
On-site laboratory clinical laboratory parameters [4]	X				X	
Blood samples for PK subgroup				[X] [10]		
Vital signs (BP, PR, BT, BOS) [5]		X		X	X	
Body weight		X				
12-lead ECG [9]		X		X	X	
IMP injection			X			
Images acquisition			X			
IWRS [6]	X	X				
Adverse events (AEs) [7]	X					
Concomitant treatments	X					
Procedures/Therapeutic measures	X					
Record of histopathology results and patient's diagnosis						X

(1) V1 can be performed on the same day as V2.

(2) Physical examination is to be performed by a physician: examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information indicating the global assessment (normal or abnormal (specify)) of the physical examination has to be recorded on source documentation.

(3) Urine pregnancy test (if applicable) is to be done on site. Results must be available prior to IWRS connection and MRI procedures and must be negative to allow administration of IMP.

(4) Clinical laboratory parameters will be analyzed by the on-site laboratory: hematology and biochemistry according to section 7.2.3.5.
eGFR is to be evaluated based on bedside Schwartz equation as described in section 7.2.3.4. Creatinine and eGFR can be done within one week before IMP administration. At V2 results must be available prior to IWRS connection and MRI procedure and must fulfill Non-inclusion criteria to allow administration of IMP.

(5) Vital signs: BP: Blood Pressure (supine systolic and diastolic), PR: Pulse Rate, BT: Body Temperature, BOS: Blood Oxygen Saturation.

(6) IWRS: at V1, the patient number will be assigned; at V2 IMP number is given and PK timepoint allocated when applicable; and any patient's screening failure or premature discontinuation will be recorded via IWRS.

(7) AEs occurring during the time of the patient's participation in the trial, must be reported and followed, unless they meet the following definition: the events which occur before the first IMP administration, and which are not serious and not related to the trial procedures may be recorded as medical history upon the investigator's judgement. Procedures/therapeutic measures for AE are also to be reported. See section 9 for further information.

(8) All the assessments performed prior to the MRI at V2 will be considered as baseline value.

(9) Triplicate ECGs (3 measurements taken at approximately 1 min intervals) that will be analyzed centrally.

(10) For PK subgroup: blood samples post-gadopiclenol injection according to sampling time windows described in Table 4. in section 8.5.3 and sent to central laboratory.

TRIAL DIAGRAMS

Figure 1: Trial diagram for adult patients

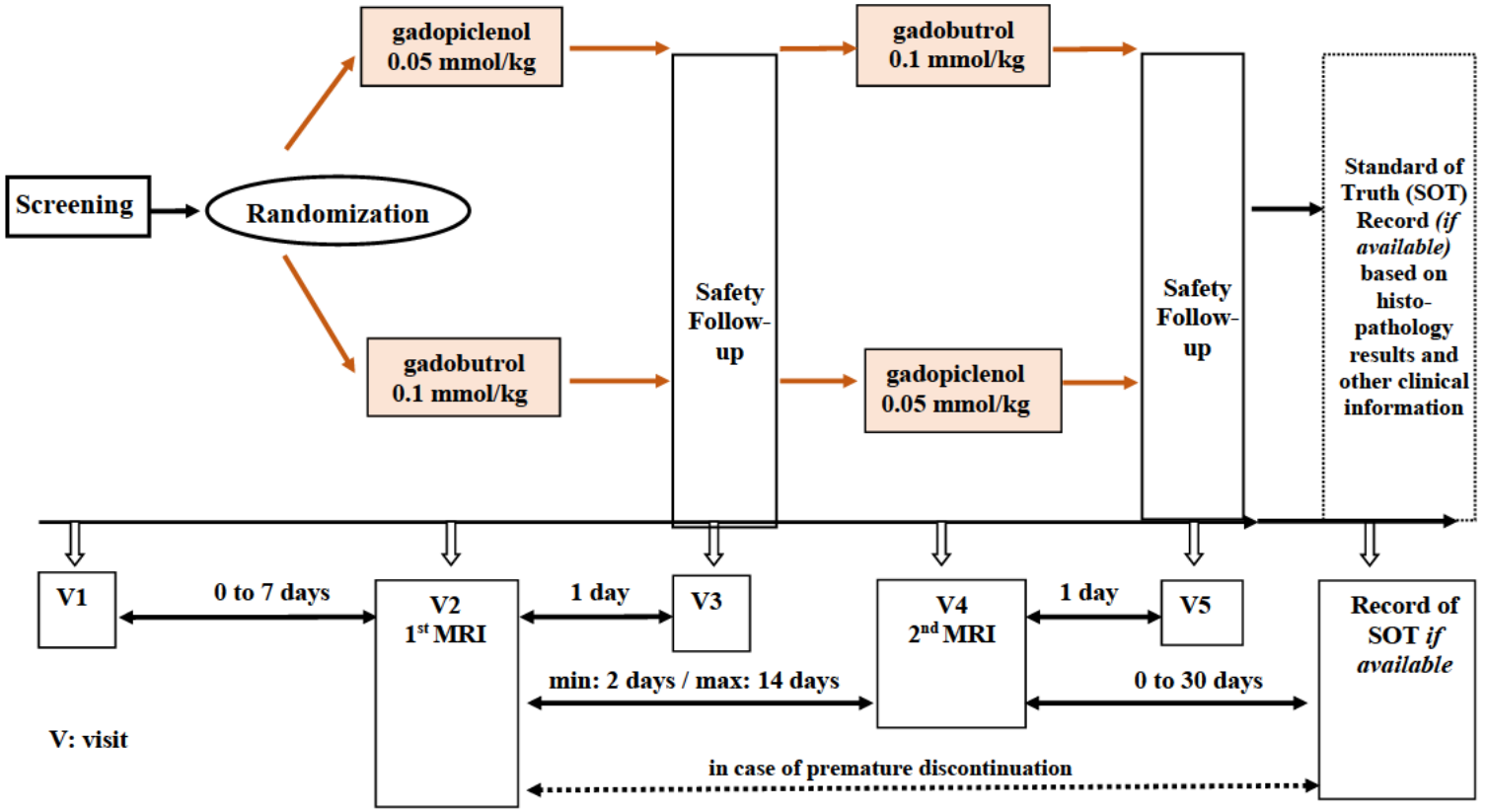
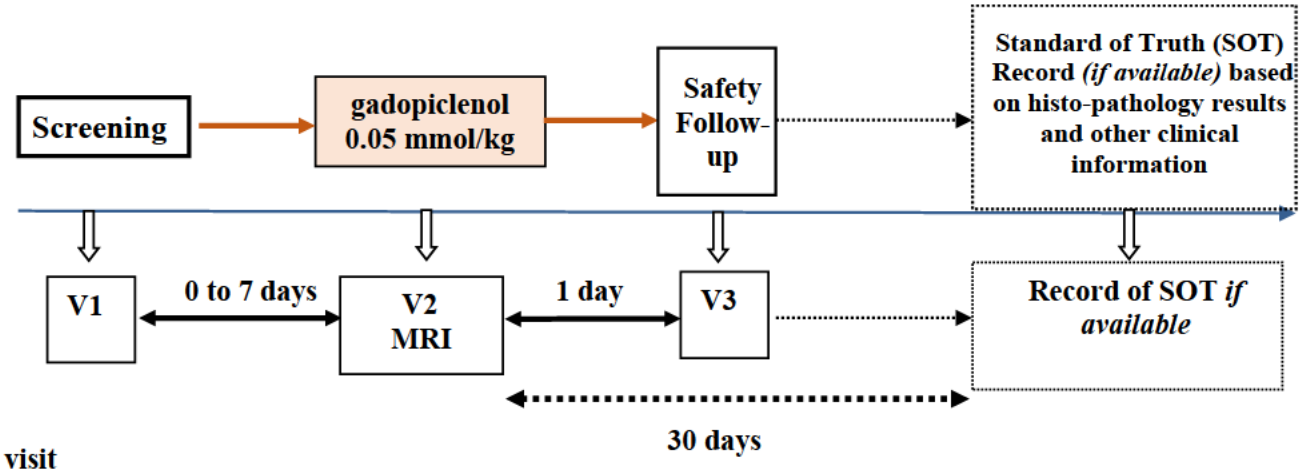


Figure 2: Trial diagram for pediatric patients



V: visit

SIGNATURE PAGE

GUERBET MEDICAL EXPERT [redacted]	Signature: [redacted] Date: DD Mon YYYY
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INVESTIGATOR STATEMENT

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

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

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
BOS	Blood Oxygen Saturation
BP	Blood Pressure
BT	Body Temperature
BW	Body Weight
CA	Competent Authority
CRA	Clinical Research Associate
eCRF	electronic Case Report Form
CNS	Central Nervous System
CRO	Contract Research Organization
EU/UK-QPPV	European/United Kingdom Qualified Person for Pharmacovigilance
ESUR	European Society of Urogenital Radiology (guidelines)
FAS	Full Analysis Set
GBCA	Gadolinium Based Contrast Agent
Gd	Gadolinium
GCP	Good Clinical Practice
IB	Investigator's Brochure
IBR	Independent Blinded Reader
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INV	Investigator / Sub-Investigator
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intra Venous
IWRS	Interactive Web Response System
MRI	Magnetic Resonance Imaging
NSF	Nephrogenic Systemic Fibrosis
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Pulse Rate

SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
SmPC	Summary of Product Characteristics
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TSRB	Trial Safety Review Board

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

AMENDMENT 2

DOCUMENT HISTORY	
Document	Date
Protocol V1.0 (internal)	08-Aug-2022
Protocol V2.0 (internal)	20-Jan-2023
Protocol V3.0	17-Feb-2023
Protocol V4.0	29-Mar-2024

Overall Rationale for the Amendment 2:

The main reason for the Amendment is to alleviate restrictions of minimum number of pediatric patients per age group and in PK cohort.

The previous version of the Protocol contained pediatric patients' distribution per age group with at least 10 patients in each age group and at least 6 patients in each age group included in the PK evaluation. Considering that the achievement of pediatric sample size (including PK subgroup) with the restricted distribution per age group is highly unlikely and the risk of having a very limited number of patients in the age group <2 years is high, the present amendment considers that expected exposure parameters for the uncompleted age groups could be predicted by simulation providing that:

1. There is no concern to combine pediatric and pre-existing data in a single population PK model;
2. The maturation of the renal function in non-Japanese children < 2years of age from the pediatric trial GDX-44-015 is appropriately incorporated in the model;
3. Reducing the sample size will not compromise the accurate evaluation of the pharmacokinetic profile of gadopiclenol in plasma.
4. The PK profile of Japanese adults is appropriately incorporated in the model.

A preliminary evaluation performed on the data collected in non-Japanese pediatrics < 2 years of age from the pediatric trial GDX-44-015, that was active at same time as the present trial, confirmed that the 3 first conditions above can be met. Moreover the large sample size available to build the global gadopiclenol popPK model will ensure high precision in parameters estimates. The 4th condition is supported by the similar concentrations and pharmacokinetic parameters observed in non-Japanese and Japanese adult healthy volunteers (trials GDX-44-003 and GDX-44-013). Consequently, the total number of patients between 12 (currently enrolled) and 24 will be acceptable without minimum number of patients per age group.

Efficacy evaluation can be performed without pediatric patients' equal distribution in age groups. Knowing that at the time of the current amendment, each age group is already represented in the pediatric cohort, any final distribution per age group will be appropriate for efficacy evaluation.

Other changes include:

- Per previous protocol versions, blood samples for PK must have been performed through different IV line. However, considering the study population, this condition seems to be an important barrier preventing from the enrolment of young children. This burden will be avoided in the current amendment and the collection of PK samples from the same line used for the IMP injection will be allowed considering that the saline flush after IMP injection will eliminate all remnants of IMP from the line.
- the possibility to perform separate statistical analysis for adults and pediatric cohorts in case the time lapse between the end of enrollment in both cohorts is more than six months.

This amendment makes changes to the following sections of the Protocol without impacting the Master patient Information and Consent Form. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis.

New text is shown in bold font and deleted text in strikethrough.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
2.2.3 Secondary objective for pediatric patients – Pharmacokinetics (PK) group	To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection in a **sub**group of ~~24~~ pediatric patients referred for contrast-enhanced MRI of CNS or Body regions.	The final number of patients in PK subgroup (between 12 and 24) is unknown until the end of the trial.
3.1.2 Pediatric cohort	An IWRS will be used to allocate the IMP to be used and to calculate the volume of IMP to be administered based on the body weight of the patient. In addition, it will guarantee an appropriate representation of the different groups of age and regions in ensuring the inclusion as follows: • ~~10 patients in each age group.~~ • Within each age group from 2 to 17 years, at least: - ~~3~~**2** patients referred for CNS MRI, - ~~3~~**2** patients referred for Body MRI, - Other ~~4~~ patients can be referred for CNS or Body MRI. A subgroup of **up to** 24 children will be included in the evaluation of PK profile in plasma after gadopiclenol administration.	To cancel the minimum number of patients in each age group and reduce minimum number by region due to enrolling difficulties in pediatric cohort. Acceptable for the reliable efficacy evaluation. The final number of patients in PK subgroup (between 12 and 24) is unknown until the end of the trial.
8.5.3 Blood sampling for PK (only for a subgroup of pediatric population)	A peripheral catheter will be placed for blood collection in the forearm ~~(contralateral to the injection site)~~ or in the feet. As far as possible a venous line already in place for the current care (central or peripheral venous catheter) will be used for	To avoid a barrier preventing the enrolment of children, considering that the saline flush after IMP injection will eliminate all remnants of IMP from the line.

Section # and Name	Description of Change	Brief Rationale
	blood collection ~~Injection and sampling must be performed through different IV lines.~~	
11.2 Sample Size **Number of patients for the pediatric cohort:**	Sample size for population of the PK analysis **is not based on statistical consideration and** has been calculated taking into consideration limitation and difficulties to collect many samples without interfering with patient care and duration of hospital stay. Based on these considerations, CO-SPONSORS ~~evaluated~~ **estimated** that 6 patients per age group, i.e., 24 patients, **in the population of the PK analysis will be sufficient to inform gadopiclenol pharmacokinetics in plasma in Japanese children** ~~would be needed to be involved in the population of PK analysis and sufficient to obtain a Japanese pediatric population PK profile~~. **In case age groups are not or partially completed, the impact of a reduced sample size on the precision of parameter estimates will not be an issue since the available data will be fitted into a model based on a large sample size and including Japanese and non-Japanese adult participants as well as non-Japanese pediatric participants. A simulation approach based on this established model enriched with available Japanese pediatric data, will be used to simulate the missing patients, if any.**	Rational added to explain why even reduced sample size will have no impact on the accuracy of exposure parameters estimation.
11.3 Planned Analysis	**The separate statistical analysis for adults and pediatric cohorts can be considered in case the time lapse between the end of enrollment in both cohorts is more than six months.**	To consider the possibility to perform separate statistical analysis for adults and pediatric cohorts.

1 INTRODUCTION

1.1 Trial Rationale

The use of gadolinium-based contrast agents (GBCAs) has revolutionized the radiologic field since their introduction more than 30 years ago. These contrast agents have been extensively used for Magnetic Resonance Imaging (MRI) in a large range of indications, particularly examinations of central nervous system (CNS). Contrast enhancement has enabled improving tissue visualization, lesion characterization, and more sensitive detection of even very small lesions.

GBCAs consist of the active substance gadolinium (Gd) and a chelating agent. They can be categorized by their chemical structures into linear and macrocyclic agents and further subdivided by their charge (ionic or non-ionic). In vitro experiments have shown that the macrocyclic compounds are the most stable, with an undetectable release of Gd3+ ions under physiological conditions [1].

Evidence from the literature have linked the exposure to Gd with two concerns: the development of Nephrogenic Systemic Fibrosis (NSF) in at-risk subjects with impaired renal function [2-4] and the potential retention of Gd in tissues even in subjects with normal renal function [5-10]. Consequently, the use of some less stable linear GBCAs more prone to release free Gd was then restricted by Health Authorities in most countries [11].

Another consequence was the development of new macrocyclic compounds referred as more stable. Among them, gadopiclenol is a new chemical entity discovered and developed by GUERBET. It is a non-ionic macrocyclic gadolinium complex, of high kinetic stability, intended to be used in human, by intravenous (IV) administration, as a contrast agent for MRI.

The ability of gadopiclenol to be an efficient MRI contrast agent has been demonstrated by its at least two-fold higher T1 relaxivity compared to other available GBCAs [12].

During the global clinical development program of gadopiclenol eight studies were conducted since 2013 (see section 1.2). In total 1047 non-Japanese patients/healthy volunteers were exposed to gadopiclenol at different doses (up to 0.3 mmol/kg), including 80 pediatric patients from 2 to 17 years of age. In addition, a phase I trial has been recently conducted on 27 Japanese adult healthy volunteers for safety and pharmacokinetic (PK) purpose.

Based on the extensive available PK, clinical efficacy and safety data, including the recent Japanese phase I trial, it is considered that there are sufficient guarantees to ensure the safety as well as the efficacy of gadopiclenol administration at the dose of 0.05 mmol/kg body weight (BW) in adult and pediatric patients from birth to 17 years of age in this phase III trial.

The present trial is part of clinical development program for NDA (New Drug Application) in Japan. It aims to study the efficacy and the safety of gadopiclenol in Japanese adult and pediatric patients from birth to 17 years of age.

1.2 Background

At the time of this protocol submission, the following clinical data in adults and pediatrics are already available:

A phase I/IIa PK single center, ascending dose trial (GDX-44-003) has been conducted on 54 healthy volunteers (gender balanced) and 12 patients with CNS disorders in Europe. The primary objective of the trial was to evaluate the safety (clinical and biological) and pharmacokinetics (plasma and urine) of gadopiclenol through a 2 days post dosing confinement period and 7 days follow-up [12].

For the phase I part of this trial, six intravenous doses ranging from 0.025 to 0.3 mmol/kg were tested in successive cohorts of 9 healthy volunteers (6 active and 3 placebo). No serious adverse events were

reported. The pharmacokinetics of gadopiclenol were considered linear, characterized by a rapid distribution into the extracellular space and subsequent fast renal excretion. The elimination half-life of gadopiclenol ranged from 1.5 to 2 hours.

For the Phase IIa part of this trial, four doses were tested in successive cohorts of 3 patients with CNS lesions: 0.05, 0.075, 0.1, and 0.2 mmol/kg, administered as single dose. All subjects underwent MRI examination. Similar gadopiclenol concentrations and pharmacokinetics were observed in patients versus healthy volunteers at corresponding doses.

A Phase IIa proof of concept trial (GDX-44-008) aimed to evaluate the diagnostic value of gadopiclenol for hepatocellular carcinoma in patients with suspected small nodules and chronic liver disease. A total of 40 patients were enrolled: 30 patients injected with the dose of 0.1 mmol/kg and 10 patients with the dose of 0.05 mmol/kg. No safety concerns have been raised from the trial.

A Phase IIb trial (GDX-44-004) has been conducted in 280 adults with CNS diseases. This was a dose-response trial with a cross-over design allowing the comparison of contrast quality provided by each of the 4 tested gadopiclenol doses (0.025, 0.05, 0.1 and 0.2 mmol/kg) towards gadobenate dimeglumine at the standard dose of 0.1 mmol/kg. No safety concerns have been raised from the trial. Gadopiclenol at 0.05 mmol/kg was identified as the lowest dose showing efficacy similar to the reference product [13].

A phase I trial in patients with renal insufficiency (GDX-44-005) included 5 successive cohorts of 8 subjects: healthy volunteers and patients with mild, moderate, severe and end stage renal disease (ESRD). Urinary and blood long term elimination were evaluated up to 6 months following gadopiclenol injection at a dose of 0.1 mmol/kg. The study showed a good safety profile of gadopiclenol. After a single intravenous injection, gadopiclenol is eliminated predominantly by renal clearance: the elimination half-life is increasing with the degree of renal impairment (mean t1/2 of 1.9 h, 3.3 h, 3.8 h and 11.7 h in cohort 1 (healthy volunteers), 2 (patients with mild renal impairment), 3 (patients with moderate renal impairment) and 4 (patients with severe renal impairment), respectively. In ESRD patients, the first hemodialysis session effectively removed 95% to 98% of gadopiclenol concentration from the plasma.

A phase I QT/QTc trial (GDX-44-006) has been conducted in 48 volunteers to assess the cardiac safety of gadopiclenol tested at 2 doses (0.1 mmol/kg and 0.3 mmol/kg) with positive control. Urinary and blood long term elimination was evaluated up to 3 months after the injection. The trial demonstrated that gadopiclenol did not prolong the QT interval neither at the dose of 0.1 mmol/kg nor at the dose of 0.3 mmol/kg in healthy volunteers. The clinical and biological safety profile of the product observed during the study did not raise any concern [14].

A phase II trial (GDX-44-007) was conducted in 80 pediatric patients (aged 2 to 17 years) with CNS and Body pathologies. The population PK analysis showed no indication for dose adaptation based on age in addition to body weight-based dosing. Positive efficacy results were obtained, and a good clinical and biological safety profile was observed during the study (up to 3 months follow-up period after injection).

Two randomized phase III trials were conducted, including 256 randomized patients for GDX-44-010 CNS trial and 304 randomized patients for GDX-44-011 body trial. Efficacy of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of lesion visualization was demonstrated for both trials and a good safety profile was observed.

A phase I trial (GDX-44-013) on 27 Japanese adult healthy volunteers was recently completed. It was performed to assess the PK and safety of gadopiclenol in Japanese population. No SAE and no IMP or study discontinuation due to TEAE were reported. The pharmacokinetic of gadopiclenol was linear in the dose range 0.025 to 0.1 mmol/kg as single dose in healthy Japanese volunteers. Similar concentrations and pharmacokinetic parameters were observed in a previous study in non-Japanese healthy volunteers (GDX-44-003).

The clinical and biological safety profile of gadopiclenol observed during these 9 studies did not raise any safety concern. More details on the safety are provided in the Investigator's Brochure (IB) in force that is the reference safety information for gadopiclenol.

A phase II study evaluating gadopiclenol pharmacokinetics, safety, and efficacy in pediatric patients less than 2 years of age undergoing contrast-enhanced MRI is currently conducted in Europe and the USA.

1.3 Benefit/Risk Assessment

Based on the available results of the above-described trials performed with gadopiclenol outside Japan, the Benefit/Risk ratio for non-Japanese subjects/patients can be considered as positive. Taking also into account the preliminary results of the phase I PK trial conducted on adult Japanese healthy volunteers, no serious safety concern is expected to occur for the Japanese adult and pediatric patients from birth to 17 years of age who will be enrolled in the present trial.

2 TRIAL OBJECTIVES (J-GCP Article 7, Paragraph 1, Item 5)

2.1 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 adult patients referred for contrast-enhanced MRI of Central Nervous System (CNS) or Body regions.

2.2 Secondary Objectives

2.2.1 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 (thorax, abdomen, pelvis, musculoskeletal) 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 0.1mmol/kg BW based on clinical and biological parameters.

2.2.2 Secondary objective for pediatric patients

To evaluate the efficacy of gadopiclenol-enhanced MRI compared to unenhanced MRI in terms of lesion visualization.

To evaluate the safety of gadopiclenol based on clinical including ECG and biological parameters.

2.2.3 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.

2.2.4 Secondary objectives for all patients

To evaluate the diagnostic performance (sensitivity, specificity) of gadopiclenol-enhanced MRI 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.

3 TRIAL DESCRIPTION (J-GCP Article 1, Paragraph 1, Item 77)

3.1 Protocol 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, multi-center, randomized, double-blind, controlled, and cross-over design.
- The cohort of pediatric patients has a prospective, multi-center, non-randomized, open-label and single arm design.

3.1.1 Adult cohort

Adult patients, once informed consent form (ICF) signed, will perform a screening visit (V1) to confirm their eligibility for the study, then will be randomized in a 1:1 ratio to one of 2 series 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. Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the last MRI examination and other clinical information. (see Figure 1).

An Interactive Web Response System (IWRS) will be used to allocate the Investigational Medicinal Product (IMP) and to calculate the volume of IMP to be administered based on the patient's body weight. In addition, it will guarantee an appropriate representation of the different regions in ensuring the inclusion of:

- At least 80 patients referred for CNS MRI
- At least 80 patients referred for Body 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.

3.1.2 Pediatric cohort

The inclusions will be divided into 4 groups: patients from birth to 23 months of age inclusive, patients from 2 to 6 years, patients from 7 to 11 years and patients from 12 to 17 years. The recruitment in the 3 older groups of pediatric patients can be conducted in parallel with adult patients' enrolment. The decision to start the inclusion in the group of patients aged from birth to 23 months will be taken by the Trial Safety Review Board (TSRB) based on safety assessment of the first 50 adult patients and the first 10 children enrolled in the other groups including at least 3 patients from the young children group (aged from 2 to 6 years), as well as GDX-44-015 study data in non-Japanese pediatric patients aged < 2 years old.

Pediatric patients, once informed consent form (ICF) signed by the parent(s) or legal guardian(s) (where applicable), will perform a screening visit (V1) to confirm trial eligibility, then will undergo one MRI examination with gadopiclenol (V2) followed by a safety visit (V3) performed 1 day after the MRI visit. Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the MRI examination and other clinical information. (see Figure 2).

An IWRS will be used to allocate the IMP to be used and to calculate the volume of IMP to be administered based on the body weight of the patient. In addition, it will guarantee an appropriate representation of the different groups of age and regions in ensuring the inclusion as follows:

- Within each age group from 2 to 17 years, at least:
  - 2 patients referred for CNS MRI,
  - 2 patients referred for Body MRI,
  - Other patients can be referred for CNS or Body MRI.

A subgroup of up to 24 children will be included in the evaluation of PK profile in plasma after gadopiclenol administration. The approach implemented for PK analyses allows sparse blood sampling only and is selected to minimize the clinical burden to children (Refer to section 8.5.3.).

3.1.3 All patients

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

During the trial, the safety of the patients will be monitored and assessed based on the reporting of adverse events (AEs), including vital signs, ECG for pediatric patients, and clinical laboratory parameters (blood samples).

Assessment will be done off site by prospective evaluation of the images in a centralized manner. All images will be sent to a core laboratory, which will prepare the images for evaluation. This evaluation will be performed by 3 independent blinded radiologists per anatomical region. Independent blinded radiologists will be assigned to CNS or any Body regions according to their expertise. Furthermore, to allow exact matching of lesions between imaging modalities (between Pre and Paired of each contrast agent and between Paired of both contrast agents for Adults) and across readers, an independent radiologist (lesion tracker) will perform lesion tracking. In addition, images will be evaluated by the on-site investigators.

3.2 Justification for Dose

The safe and lowest effective clinical dose identified in phase IIb trial and confirmed by the results of 2 phase III trials conducted outside Japan is 0.05 mmol/kg body weight (BW).

The Phase IIb trial (GDX-44-004) was a dose-response trial allowing the comparison of contrast quality provided by 4 tested gadopiclenol doses (0.025, 0.05, 0.1 and 0.2 mmol/kg) towards gadobenate dimeglumine at the standard dose of 0.1 mmol/kg. Gadopiclenol at 0.05 mmol/kg was identified as the lowest dose showing efficacy like the reference product.

The two Phase III trials (GDX-44-010 and GDX-44-011) demonstrated that gadopiclenol at the dose of 0.05 mmol/kg BW is as efficient as gadobutrol at clinical dose of 0.1 mmol/kg BW. It was assessed in adult patients for lesion visualization in patients with known or suspected enhancing abnormality(ies) and/or lesion(s) in one region among CNS, head & neck, thorax (including breast), abdomen (including

liver, pancreas, and kidney), pelvis (including uterus, ovary, and prostate) and musculoskeletal system (including extremities).

Efficacy of gadopiclenol at the dose of 0.05 mmol/kg BW was also shown in the phase II trial GDX-44-007 conducted in pediatric patients from 2 to 17 years of age.

Pharmacokinetic profile of gadopiclenol in adult Japanese subjects was demonstrated as linear in the phase I trial GDX-44-013. Similar concentrations and pharmacokinetic parameters were observed as in non-Japanese healthy volunteers (GDX-44-003 study). The exposure to gadopiclenol is similar in Japanese and non-Japanese subjects and suggests that there is no need for dose adjustment of gadopiclenol in Japanese patients.

In addition, the safety profile of gadopiclenol at the dose of 0.05 mmol/kg BW was shown in the 4 trials specified above.

Consequently, the dose of gadopiclenol chosen for this trial will be 0.05 mmol/kg BW.

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

3.3 Trial Duration

3.3.1 Duration of patients' participation

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

3.3.1.1 Trial duration for adult patients

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

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

Maximum trial duration for collection of data: 53 days, if the screening period lasts 7 days, the second MRI is done 14 days after the first one, and patient's diagnosis as a standard of truth is collected within 30 days after the second MRI.

The trial includes a maximum of 5 visits and the record of patients' diagnosis as standard of truth:

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

Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the last MRI examination and other clinical information.

3.3.1.2 Trial duration for pediatric patients

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

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

Maximum trial duration for collection of data from the patients: 39 days, if the screening period lasts 7 days, and patient's diagnosis as a standard of truth is collected within 30 days after the MRI.

The trial includes a maximum of 3 visits:

- One screening visit (V1) up to 7 days prior to the imaging visit V2 (V1 can be done on the same day as V2, if all inclusion/non-inclusion criteria are met).
- One imaging visit (V2): will consist of gadopiclenol injection and MRI procedure. For PK sub-group: blood sampling for PK analyses will start during V2 after IMP injection and will take up to 8 hours.
- One safety visit (V3): 1 day after gadopiclenol injection and MRI examination.
  Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the MRI examination and other clinical information.

Patient's diagnosis as standard of truth will be recorded if available based on histopathology results from a biopsy or a surgery up to 30 days after the last MRI examination and other clinical information.

3.3.2 End of trial

The trial is considered as completed once all the images collected for all the patients have been reviewed by all independent blinded readers and the standard of truth (if available) have been obtained.

3.4 Interim Analysis

Not applicable.

3.5 Trial Committee

Trial Safety Review Board (TSRB) described in section 12 is established to decide to start the enrollment of infant's group in the trial based on the safety assessment of the first 50 adult patients and the first 10 children including at least 3 patients from the young children group (aged from 2 to 6 years), as well as GDX-44-015 study data in non-Japanese pediatric patients aged < 2 years old.

4 PATIENT SELECTION (J-GCP Article 7, Paragraph 8)

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

4.1 Inclusion Criteria

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

4.1.1 Inclusion criteria for all patients

1.All Patient presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in CNS or in at least one body region among head & neck, thorax (e.g. breast), abdomen (e.g. liver, pancreas, and kidney), pelvis (e.g. uterus, ovary, and prostate) and musculoskeletal (e.g. extremities) based on a previous imaging procedure performed within 12 months prior to ICF signature.

2.All If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of remaining enhancing abnormality(ies) and/or lesion(s) based on available clinical information.

3.All Patient able and willing to participate in the trial.

4.All Patient affiliated to national health insurance according to local regulatory requirements.

4.1.2 Inclusion criteria for adult patients

1.A Female or male adult patient having reached legal majority age of 18 years.

2.A Patient scheduled for a contrast-enhanced MRI examination of a CNS or body region for clinical reasons and agreeing to have a second contrast-enhanced MRI examination for the purpose of the trial.

3.A Patient having read the information and having provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial related procedure being conducted.

4.1.3 Inclusion criteria for pediatric patients

1.P Female or male pediatric patient from birth to 17 years.
For patients aged from birth to 27 days, only term newborn infants are eligible.
Patients may not have reached the age of 18 years at the MRI examination.

2.P Patient whose parent(s) or legal guardian (where applicable) having read the information provided his/her/their consent to patient's participation in writing by dating and signing the informed consent prior to any trial related procedure being conducted.

3.P Patient with capacity of understanding who received age- and maturity-appropriate information and provided his/her assent to participate in the trial.

4.1.4 Additional inclusion criterion for pediatric patients participating in PK group

Inclusion criteria 1.P – 3.P for pediatric patients specified under 4.1.3 apply.
Additional Inclusion criterion for participation in PK group:

4.P-PK Patient and his/her parent(s) or legal guardian (where applicable) having marked and signed in the Informed Consent form or respectively in the patient assent form their consent to participate in the PK subgroup analyses.

4.2 Non-Inclusion Criteria

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

4.2.1 Non-inclusion criteria for all patients

1bis.All Patient referred for contrast-enhanced cardiac MRI as primary examination (e.g. imaging protocol requiring stress or more than a single injection of gadolinium contrast agent) except for late-enhancement cardiac imaging.

2.All Patient having received any investigational medicinal product within 7 days prior to trial entry or scheduled to receive any investigational treatment in the course of the trial.

3.All Patient presenting with any contraindication to MRI examinations.

4.All Patient having received any contrast agent (for MRI or CT) within 3 days prior (or 7 days for patients < 1year old) to trial product administration or scheduled to receive any contrast agent during the course of the trial or within 24 hours after the last trial product administration (or 7 days after for patients < 1 year old).

5.All Patient with anticipated, current or past condition (medical, psychological, social, or geographical) that would compromise the patient's safety or her/his ability to participate in the trial in the Investigator's opinion.

6.All Female patient of childbearing potential with positive urine pregnancy test done within 1 day prior to each contrast agent administration and not able / not willing to use highly effective birth-controlled method* during the trial duration.

Female must have effective medically approved contraception until the last trial visit, if of childbearing potential or with amenorrhea for less than 12 months or must be surgically sterilized or post-menopausal (> 2 years amenorrhea).

7.All Patient unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the trial.

8.All Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

9.All Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other GBCAs (such as hypersensitivity, post contrast acute kidney injury).

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

4.2.2 Non-inclusion criteria for adult patients

1.A Patient with acute disease that may rapidly evolve between the 2 MRI examinations

2.A Patient previously randomized in this trial.

3.A Patient expected/scheduled to have any treatment or medical procedure (e.g., chemotherapy, radiotherapy, biopsy or surgery etc.).) that may impact the aspects of the imaged lesions between the 2 MRI examinations. (Patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included).

4bis.A Patient presenting an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² (based on Japanese coefficient-modified CKD-EPI formula) assessed within one week prior to the first contrast agent administration.

4.2.3 Non-inclusion criteria for pediatric patients

1.P Patient with previously attributed IMP number in this trial.

2.P Patient with known long QT syndrome.

3.P Patient presenting an estimated Glomerular Filtration Rate (eGFR) outside age-adjusted normal ranges (based on bedside Schwartz equation) assessed within one week prior to contrast agent administration

4.3 Patient Identification

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

Information concerning participation in the PK analyses cohort is specified in the Patient' parent(s) or legal guardian (where applicable) consent form. The consent to participate in the PK analyses must be marked and signed in the Informed Consent Form, after having read and understood the related information.

Any patient who has signed an informed consent or who's parent(s) or legal guardian (where applicable) signed an informed consent will be considered as a 'screened' patient.

This patient ID will contain 8 digits: the first three digits corresponding to the country number (code ISO 3166-1 numeric 392) the following two digits corresponding to the site number, which are attributed at the beginning of the trial, and the last three digits being chronologically implemented depending on patient screening. The lowest screening number will correspond to the first patient screened at this site and the highest number to the last patient screened.

5 INVESTIGATIONAL MEDICINAL PRODUCTS (J-GCP Article 7, Paragraph 1, Item 6)

Investigational Medicinal Product(s) (IMP) will be manufactured, labeled, packaged, and released in accordance with:

- J-GCP; MHLW No. 161, 28 December 2012
- European Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals

In addition, the IMP manufacturing, packaging, labeling and release will comply with any local applicable regulatory requirement.

The IMP will consist of 1 vial packaged in a carton box with a single use detachable label that will allow ensuring accuracy of IMP allocation per patient.

5.1 Investigational Medicinal Product(s) Description

5.1.1 Investigational Medicinal Product 1

Name: gadopiclenol (formulation G03277.100)

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

Concentration: 0.5 mmol/mL

Route and method of administration: single intravenous (IV) bolus injection at a recommended rate of approximately 2 mL/second followed by a 0.9% saline flush via manual injection or power injector

General sedation or topical anesthesia will be considered to minimize discomfort and distress (to be documented in the medical file and in the eCRF as concomitant medication).

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

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

5.1.2 Investigational Medicinal Product 2 – Adult patients only (J-GCP Article 7, Paragraph *1,r*)

Name: gadobutrol

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

Concentration: 1.0 mmol/mL

Route and method of administration: single intravenous (IV) bolus injection at a recommended rate of approximately 2 mL/second followed by a 0.9% saline flush via manual injection or power injector. The injection rate should be identical for both products and may vary depending on scanned organ/region and age of patients.

General sedation or topical anesthesia will be considered to minimize discomfort and distress (to be documented in the medical file and in the eCRF as concomitant medication).

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

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

5.2 Packaging, Labeling, Storage

Packaging and labeling will be performed in strict accordance with the local regulatory specifications and requirements.

The packaging and labeling of gadopiclenol and gadobutrol will be performed by GUERBET (or its designee).

The outer packaging will be the same for both products to ensure the double-blind conditions.

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

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

In case of issue related to IMP (damaged, broken vials…), a new IMP will be allocated to the patient via the IWRS.

All IMPs will be stored in a secure place, under the responsibility of the Investigator or other authorized individuals. The IMPs should be stored at 30°C or below.

At the time of the trial completion, all used (including empty vials) and unused IMPs should have been returned to GUERBET or to the predefined location for storage before destruction.

5.3 Condition of Investigational Medicinal Product Allocation

5.3.1 Investigational Product(s) Allocation / Randomization

5.3.1.1 For adult patients:

At V2, the patients will be randomly and in blinded manner assigned to one series of 2 MRIs performed each at two trial visits separated by a wash out period of 2 days minimum and up to 14 days. One series consists of the use of gadopiclenol, single intravenous (IV) bolus injection, as contrast agent at V2 and gadobutrol, single intravenous (IV) bolus injection, at V4 and reverse order for the second series (see Figure 1).

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

The randomization to determine the order of injection at V2 and V4 will be done via IWRS and performed in blocks to prevent unequal treatment allocation.

An initial shipment of IMPs will be sent to the investigational sites after having received regulatory authorization(s)/ethical approval(s) as per local requirements. Additional shipments will be sent according to patient recruitment progress of a given investigational site. The site should ensure to have enough IMPs before including a new patient. IMP receipt will be acknowledged by the investigator (or any designated person in his/her team).

At V2 and V4, once all the inclusion / non-inclusion criteria have been checked, the site should log onto the IWRS which will allocate IMP(s) number available at the site. This/these IMP(s) will correspond to the allocated treatment arm and to the contrast medium allocated for the enhanced MRI procedure.

5.3.1.2 For pediatric patients:

At V2, the patients will be allocated in an open-label way to an IMP corresponding to a vial of gadopiclenol for a single intravenous (IV) bolus injection, as contrast agent at V2 (see Figure 2).

An initial shipment of IMPs will be sent to the investigational sites after having received regulatory authorization(s)/ethical approval(s) as per local requirements. Additional shipments will be sent according to patient recruitment progress of a given investigational site. The site should ensure to have enough IMPs before including a new patient. IMP receipt will be acknowledged by the investigator (or any designated person in his/her team).

At V2, once all the inclusion /non-inclusion criteria have been checked, the site should log onto the IWRS which will allocate IMP number available at the site.

5.3.1.3 For all patients:

In case one IMP breaks, becomes non-sterile, is not available, has had storage temperature excursion or any problem of IMP allocation (e.g., wrong IMP administered to the patient), the site must immediately report the incident into IWRS and to GUERBET's representative to ensure that all corrective actions are taken. Corrective actions may include transferring the IMP to quarantine to prevent further IMP

allocation by the site until the situation is under control again. Detailed instructions can be found in the IWRS manual provided to the sites.

5.3.2 Double-Blind Conditions

For the adult patients' cohort, the trial design and the injection of the IMPs require previous identification of two separate teams in each site before the trial start. One team will manage the blinded data and the other one will be unblinded and will be in charge of the IMPs preparation and administration. The unblinded staff will have to document in a separated patient's file all the unblinded information related to the IMPs. Only blinded data will be entered in the clinical eCRF pages.

During the trial, the two teams should not exchange any information regarding the IMPs (volume, nature of IMP injected, order of administration). The patients' files with unblinded data should not be filed with the patient's medical and trial files to avoid unblinding. The unblinded documentation should be stored shielded from the view of the blinded staff.

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

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

Image readings of all patients will be evaluated in blinded conditions regarding the contrast agent injected and the image modality (Paired and Pre), as described in section 8.4

5.3.3 Individual Trial Treatment Unblinding – Adult patients only

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

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

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

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

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

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

Please refer to section 9.5 for detailed information on patients' safety monitoring.

5.4 Investigational Medicinal Product Management

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense IMP(s) is responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by GUERBET and in accordance with the applicable regulatory requirements.

Any quality issue noticed with the receipt or use of an IMP (deficient IMP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to GUERBET, who will initiate a complaint procedure.

Under no circumstances shall the investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

5.5 Auxiliary Medicinal Product(s) and Other Trial Products

Not applicable

5.6 Trial Product(s) Compliance and Accountability

An unblinded third party, the investigator, the hospital pharmacist, or other allowed personnel, designated by the investigator, will keep accurate records of IMPs accountability at site level as well as accurate records of the batch numbers and quantities of the IMP given to each patient.

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

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

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

For the children cohort, the volume of gadopiclenol to be administered will be rounded to one decimal and calculated based on patient's BW with one decimal fraction.

6 CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

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

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

6.1.1 Concomitant Medications of Special Attention

Currently, no treatment has been identified that can prevent an allergic reaction with any GBCA. Thus, no pre-treatment of any nature will be recommended before contrast-enhanced MRI. Nevertheless, if the investigator decides to premedicate a patient, the treatment must be documented in the medical file and then in the clinical eCRF. Considering the pediatric patients, treatments used for general sedation or topical anesthesia or other nonpharmacological methods (using feed and swaddle, etc) will be set up according to the current practice at site.

In general, there are no specific recommendations regarding GBCAs, and therefore, no specific hydration procedure is defined in this protocol. Nonetheless, whenever possible, the patient should be encouraged to drink water and other non-alcoholic fluids liberally before and after the injection.

According to current knowledge, there is no other concomitant treatment of special attention for this trial. However, warnings and precautions for use of the concomitant treatments taken by the patient should be considered.

In addition, for adult patients, any treatment or medical procedure (e.g., chemotherapy, radiotherapy, biopsy, or surgery etc.…) which may impact the appearance of lesion of the imaged region between the 2 MRI examinations should be avoided. However, patients under corticosteroids and/or maintenance chemotherapy with a stable dose at the time of screening visit and throughout the trial can be included.

6.1.2 Prohibited Concomitant Medications

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

6.2 Concomitant Procedures

Not applicable

7 EVALUATION CRITERIA

An overview of the imaging trial criteria evaluated by the investigator (INV) and the Independent Blinded Readers (IBR) is provided in Table 3 below:

Table 3: Overview of imaging trial criteria

Population	**Adult and Pediatric Patients**	**Adult Patients**	**Adult and Pediatric Patients**	**Adult Patients**	**Adult Patients**
Images	**Pre gadopiclenol**	**Pre gadobutrol**	**Paired gadopiclenol**	**Paired gadobutrol**	**Global matched-pairs**
Lesion visualization	IBR	IBR	IBR	IBR	
Technical adequacy of images	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Size of lesions (Adults)	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Location of lesions (Adults)	INV/IBR	INV/IBR	INV/IBR	INV/IBR	IBR
Number of lesions (Adults)					IBR
Number, size and location of lesion (Pediatric cohort)	INV/IBR		INV/IBR		
Diagnostic confidence and patient's diagnosis	INV/IBR	INV/IBR	INV/IBR	INV/IBR	
Patient management plan			INV (Adult)	INV	
Contrast to Noise Ratio (CNR) – CNS only					IBR
Percentage enhancement (E%) of lesion					IBR
Lesion to Background Ratio (LBR)					IBR
Overall diagnostic preference					IBR

INV: Investigator or Sub-Investigator (on-site)

IBR: Independent Blinded Readers (off-site)

Pre gadobutrol and paired gadobutrol evaluation: not applicable for pediatric patients

7.1 Co-Primary Criteria – Adult Patients Only (off-site read)

o Lesion visualization on Paired Images

The lesion visualization criterion is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement assessed by 3 independent off-site blinded readers (IBR).

The IBR will record each of the 3 co-primary criteria for up to 10 largest and most enhancing lesions on Paired (pre+post) images performed with gadopiclenol and Paired (pre+post) images performed with gadobutrol as described below.

- **Border delineation:**

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

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

- **Internal morphology:**

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

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

- **Degree of contrast enhancement:**

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

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

For each co-primary criterion, a mean of scores will be calculated as follows:

Mean of scores = (score of lesion 1 + score of lesion 2 (if any) … + score of lesion n (if any) divided by the number of lesions (up to 10 lesions).

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

7.2 Secondary Criteria

7.2.1 For adult patients

7.2.1.1 Overall diagnostic preference (off-site read on global matched pairs)

The evaluation will be performed in a global matched-pairs fashion. For each patient who received the two different IMPs, Paired images from the first MR examination labeled as examination 1 will be displayed simultaneously with the corresponding Paired images from the second MR examination labeled as examination 2 and assessed by the same 3 independent off-site blinded readers (IBR).

The assessment will be scored here below:

1 = When examination 1 is preferred to examination 2
0 = When no preference is observed
2 = When examination 2 is preferred to examination 1

IBRs need to select one or more of the following six reasons for this preference:

- Contrast enhancement was superior
- Delineation of normal structure was better
- Delineation of at least one lesion was better
- Internal structure of lesions was better visualized
- More lesions were identified (In that case, the clinical impact on patient management will be assessed by the reader)
- Diagnostic confidence was greater (specify one or more reason(s): detection of lesions, characterization of disease, assignment of a grade to disease, definition of extent of disease, or other reasons that had to be specified)

7.2.1.2 Quantitative efficacy criteria (off-site read on global matched pairs)

The 3 quantitative criteria (CNR, E%, LBR) will be calculated at patient level, assessed on each paired MR examinations, in averaging the parameter for up to the 3 largest most homogeneously enhancing lesions.

- **Contrast to Noise ratio (CNR) in patients referred for CNS MRI only**

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

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

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

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

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

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

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

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

7.2.1.3 Patient management plan (on site on global matched pairs)

On-site radiologists will specify any prediction of change in the patient management between the two Paired MRIs on a global matched pairs fashion, blinded to the products.

7.2.2 For all patients: Qualitative efficacy criteria

7.2.2.1 Lesion visualization on Paired Images and Pre Images (off-site read)

The lesion visualization criterion is based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement assessed on the images acquired during the MRI performed with gadopiclenol assessed by 3 independent off-site blinded readers (IBR).

The IBR will record each of the 3 co-primary criteria for up to 10 largest and most enhancing lesions on Paired (pre+post) images and Pre images performed with gadopiclenol. Definitions of each co-primary criterion and score calculation are provided in section 7.1.

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

All pre- and paired images will be evaluated as technically adequate for diagnosis by investigators and IBR.

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

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

If non-diagnostic 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.

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

For the pediatric cohort, the investigator and the IBR have to record the number of lesions on Pre and Paired images for gadopiclenol (record either exact number when ≤ 10 lesions or > 10). The largest diameter and the location for up to 10 lesions will be recorded.

For the adult cohort,:

- for pre and paired for each MR exam during the session of visualization assessments. The largest diameter and the location will be recorded for up to 10 lesions by the IBR.
- for global matched pairs reads, IBR will record either exact number when ≤ 10 lesions or > 10. When ≤ 10 lesions are detected on one of the MRI exams, IBR will record lesion location and assess whether the same lesions are detected on both MRI exams, or whether one or more lesions are detected on one single MRI exam. When > 10 lesions detected on both MRI exams, lesion mapping will be done for up to 10 lesions and lesion location will be recorded, counting will be stopped, no further mapping is needed.
- For on-site evaluations by the investigator, the investigator will record the number of lesions on Pre and Paired images for both MRI exams (record either exact number when ≤ 10 lesions or > 10). The largest diameter and location of up to 10 lesions will be recorded.

7.2.2.4 Diagnostic confidence and patient's diagnosis (on-site and off-site read)

The investigator and IBR will record his/her diagnosis and his/her confidence in diagnosis for each patient for each Pre and Paired images of each contrast agent.

Diagnostic confidence will be evaluated to determine the level of certainty assigned to a diagnosis. This is defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a patient.

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

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

When diagnosis is not assessable, the degree of confidence is not assessed.

7.2.2.5 Patient's diagnosis as per standard of truth (based on histopathology results and other clinical information) if available

Histopathology results of a biopsy or a surgery, performed within 30 days after the last MRI examination will be collected at lesion level if any.

Final patient's diagnosis as per standard of truth based on histopathology results and other clinical information if available will be collected at patient's level if available.

7.2.3 For all patients: Safety criteria

The safety profile of gadopiclenol (both cohorts) and gadobutrol (adult cohort only) will be assessed based on the reporting adverse events (AEs), results of vital signs (and 12-lead ECG for pediatric patients), and clinical laboratory parameters (blood samples).

7.2.3.1 Adverse events

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

7.2.3.2 Vital signs

Vital signs (supine systolic and diastolic blood pressures, pulse rate as well as for pediatric patients' body temperature, blood oxygen saturation) will be measured on site and recorded according to the following schedules:

- Prior to each contrast agent injection (V2 is considered as baseline value)
- Between 30 and 75 minutes following each contrast agent injection
- One day after each contrast injection

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

7.2.3.3 ECG monitoring for pediatric patients

Triplicate ECGs (3 measurements taken at approximately 1-minute intervals) will be recorded after a rest of 5 minutes via an ECG device supplied by the ECG core laboratory.

The following parameters will be measured in supine position prior to MRI, between 30 and 75 minutes after IMP injection and one day after the IMP injection:

- Heart rate
- Intervals: RR, PR, QRS, QT [corrected QT (QTc) will be calculated according to Fridericia and Bazett methods]
- ST segments, T-wave morphology, U-wave
- Global morphology

All ECGs will be independently reviewed by a central reader (independent reviewer). Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the Site ECGs Manual.

A notable QTc change is defined as a QTc (Fridericia's or Bazett's) interval greater than 450 ms for males and females or an increase of >30 ms from baseline. All such ECGs will be flagged by the core laboratory's cardiologist and require assessment for clinical relevance by the Investigator and if clinically significant to be reported as AEs, as per investigator's judgement.

The investigator would have to give an overall interpretation of the ECG at each time point. All clinically significant abnormal changes will be recorded as AEs as per investigator's judgement. Any clinically significant abnormal changes from baseline (prior to the MRI) must be followed until the abnormality is resolved or is adequately explained.

7.2.3.4 Laboratory parameters for inclusion

Serum creatinine and estimated Glomerular Filtration Rate (eGFR) will be obtained from on-site laboratory of each site within one week prior to MRI.

For adult patients, eGFR value is to be calculated based on Japanese coefficient-modified CKD-EPI formula expressed in mL/min/1.73 m^2 [15, 16]:

- Male: $GFR = 141 \times \min(sCR/0.9, 1)^{-0.411} \times \max(sCR/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 0.813$
- Female: $GFR = 144 \times \min(sCR/0.7, 1)^{-0.329} \times \max(sCR/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 0.813$

where:
sCR is serum creatinine in mg/dL
min indicates the minimum of sCR/κ or 1
max indicates the maximum of sCR/κ or 1

For pediatric patients, eGFR value is to be calculated based on bedside Schwartz equation expressed in mL/min/1.73 m^2 [17-19]:

- eGFR (ml/min/1.73 m2) = (0.413 × Height in cm) / Standardized Serum creatinine (mg/dl)

with creatinine methods with calibration traceable to isotope dilution mass spectroscopy (IDMS).

7.2.3.5 Clinical laboratory parameters

The following parameters will be obtained and assessed centrally for adult patients (at V2 V3 V4 and V5) and by on-site laboratory for pediatric patients (At V1 and V3):

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

Each laboratory will flag laboratory values falling outside of the normal ranges on the laboratory report (which the investigator should review and sign off).

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

Post-contrast acute kidney injury (PC_AKI) is defined as an increase in serum creatinine > 0.3 mg/dl (or > 26.5 µmol/l), or > 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent. Such changes will be monitored, and additional information may be requested to the Investigator. It is up to investigator to evaluate any change in serum creatinine within trial period as AKI or clinically significant or not.

7.2.4 For PK group: Pharmacokinetic level in plasma

Gadopiclenol pharmacokinetics in plasma will be assessed in both by age group and overall based on following pharmacokinetic parameters determined from the population PK model:

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

Gadopiclenol concentrations in plasma will be determined using a validated liquid chromatography coupled with tandem mass spectrometry LC-MS/MS method.

A separate analytical protocol will describe the gadopiclenol assays in plasma. Those assays will be performed by an external third party laboratory.

7.2.5 Time Point for Data Evaluation

Data will be evaluated as soon as data collection for any of the patient cohorts, either of adult or of pediatric patients, has been completed.

8 TRIAL SCHEDULE AND PROCEDURES

8.1 Trial/Study Schedule

The schedule of timepoints and events to be performed is given in the following flow charts:

Table 1: Trial flow chart for adult patients

Table 2: Trial flow chart for pediatric patients

Table 4: Time Window and Sampling Time Subgroups for PK Sampling

8.1.1 Screening Visit – V1

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

For adult patients:

- Written informed consent will be obtained from the adult patients at this visit the latest, as described in section 13.3;

For pediatric patients:

- The pediatric patients with capacity of understanding will receive age- and maturity-appropriate information about his/her participation in the trial and his/her assent to participate in the trial will be obtained at this visit the latest);
- Written informed consent for the participation of the pediatric patients in the trial prior to any trial related procedure will be obtained from their parent(s) or legal guardian (where applicable) at this visit the latest as described in section 13.3;
- Blood samples will be collected and analysed by on-site laboratory for safety assessment according to section 7.2.3.5.
  Blood samples can be done within one week prior to MRI.

For all patients:

- An Identification Number will be attributed to each patient via IWRS (see section 4.3)
- Checking of all eligibility criteria
- Recording of demographic data: sex, race, age (in years for adult patients, in years and months for pediatric patients except for children from birth to 23 months of age for whom date of birth can be collected), and patient's height
- Documentation of relevant medical history/current medical condition present before signing the informed consent including the disease justifying the MRI
- Recording of patient's history of previous exposure to any GBCA: previous intolerance has to be collected
- Documentation of the last CT, MRI or other imaging procedure documenting the region planned to be imaged dated less than 12 months prior to trial MRI
- A routine physical examination (performed by a physician) including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological
- Review and recording of concomitant treatments
- IWRS connection for recording the patient screening visit and to ensure an appropriate representation of the different regions (and ages for pediatric patients). This means that the patient's inclusion may be refused due to the region planned to be imaged or age of the pediatric patient.
- Blood sample collection for local dosage of serum creatinine and evaluation of eGFR.
  - For adult patients: eGFR value based on Japanese coefficient-modified CKD-EPI formula should be ≥ 30 mL/min/1.73 m²;
  - For pediatric patients: eGFR value based on bedside Schwartz equation should be within age-adjusted normal ranges.

  Blood sample collection for local dosage of serum creatinine and evaluation of eGFR can be done within one week prior to MRI Results must be available prior to MRI examination to check eligibility criteria. It is acceptable to use eGFR results prior trial informed consent if available within 7 days prior MRI.

- First trial MRI visit and examination needs to be scheduled within 7 days (or can be performed on the same day as V1 if all the inclusion/non-inclusion criteria are met).
- For all patients: If during the trial a patient is screen failed or is prematurely discontinued (see section10), the new patient status should be recorded in the IWRS.

8.1.2 Randomization and Imaging Visit – V2 – 0 to 7 days after Screening Visit

8.1.2.1 Procedures at Visit 2 for all patients

Procedures to be performed prior to MRI examination:

- Checking of all the eligibility criteria.
- A urine pregnancy test will be performed for female patient of childbearing potential and must be negative.
- Measurement of vital signs (systolic and diastolic blood pressure (BP), pulse Rate (PR) as well as for pediatric patients body temperature (BT), blood oxygen saturation (BOS)), and weight.
- For pediatric patients standard 12-lead ECG (triplicate, 3 measurements taken at approximately 1 min intervals) will be recorded
- For adult patients, blood samples will be collected according to central laboratory manual for safety assessment.
- Assessment of AEs will be documented.
- Any changes in concomitant treatments / procedures / therapeutic measures since the last visit will be documented.
- IWRS connection will be done to randomize the adult patients, to obtain the IMP box number, to calculate the volume of IMP to be administered based on the body weight and to record the visit date for all patients.
- IWRS connection will be done for pediatric patients of the PK group additionally to attribute time point of blood collection within each sampling window.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required sequences specified in section 8.2.2).
- The appropriate dose/volume of gadopiclenol and gadobutrol for adult patients will be administered by IV as a bolus using preferably a power injector in a peripheral vein of the antecubital region (recommended) or in the feet. IMP injection will be followed by a 0.9% saline flush injection.
- The following information will be documented in the source document and recorded: date and time of contrast agent injection, location of injection site, actual volume administered (documentation of difference from theoretical volume), actual injection rate, overdose (if any), number of vials dispensed, number of IMP injected, injection method (power injector or manual), injection of saline flush (yes/no).

Procedures to be followed after MRI examination:

The patient will stay at the trial site for between 30 and 75 minutes after the MRI examination is completed and the following procedures will be performed:

- Vital signs (systolic and diastolic BP and PR as well as for pediatric patients BT and BOS) will be obtained once between 30 and 75 minutes after the injection of contrast agent.
- For pediatric patients standard 12-lead ECG (triplicate, 3 measurements taken at approximately 1 min intervals) will be recorded.
- Assessment of AEs will be documented, including injection site reactions.

- Use/change of concomitant treatments during the visit and since the previous visit will be documented.
- Safety follow-up visit (V3) needs to be scheduled 1 day post contrast agent injection.
- For adult patients the second MRI examination (V4) will be scheduled between 2 days and 14 days post V2.

8.1.2.2 Additional procedures at Visit 2 for pediatric patients participating in PK evaluation

Time point T0

The start of gadopiclenol administration is set as time point 0 (T0). IV catheters will be inserted (a patient IV line will be established) to have contrast agent administration and blood samples collection.

Time window W1

The following task will be performed within first time window (5 - 60 min) after gadopiclenol injection:

- Blood sample will be collected for PK analysis according to time schedule attributed per IWRS. Actual sampling time must be recorded.

Time window W2

The following task will be performed within second time window (2 – 4 hours) after gadopiclenol injection:

- Blood sample will be collected for PK analysis according to time schedule attributed per IWRS. Actual sampling time must be recorded.

Time window W3

The following task will be performed within third time window (6 – 8 hours) after gadopiclenol injection:

- Blood sample will be collected for PK analysis according to time schedule attributed per IWRS. Actual sampling time must be recorded.
- Assessment of AEs will be documented.

8.1.3 Safety Visit – V3 – 1 day after Imaging Visit

The Safety Visit V3 is performed 1 day after the MRI examination.
During this visit, the following assessments or tasks will be performed:

- Blood samples will be collected and analysed for safety assessment according to section 7.2.3.5: by on-site laboratory for children and centrally for adults (according to laboratory manual).
- Vital Signs (systolic and diastolic BP, PR as well as for pediatric patients BT and BOS) should be recorded.
- For pediatric patients standard 12-lead ECG (triplicate, 3 measurements taken at approximately 1 min intervals) will be recorded.
- Assessment of AEs will be documented, including injection-site reaction.
- Use/change of concomitant treatments / procedures / therapeutic measures will be documented.
- For adult patients, remind the patient of the date scheduled for the second MRI examination V4 – to be performed between 2 and 14 days after the first MRI.

8.1.4 For adult patients: 2nd Imaging Visit – V4 – 2 to 14 days after 1st Imaging Visit

Procedures to be performed prior to MRI examination:

- A urine pregnancy test will be performed for female patient of childbearing potential and must be negative.
- Blood samples will be collected according to central laboratory manual for safety assessment.
- Vital Signs (systolic and diastolic BP, PR) and weight have to be recorded
- Assessment of AEs will be documented, including injection-site reaction.
- Use/change of concomitant treatments / procedures / therapeutic measures will be documented.
- IWRS connection will be done to obtain the IMP box number, to calculate the volume of IMP to be administered based on the body weight and to record the date of the visit.

Unenhanced and contrast-enhanced MRI examinations:

- Unenhanced and contrast-enhanced MRI will be performed according to the required sequences specified in Section 8.2.2.
- The appropriate dose/volume of gadopiclenol and gadobutrol will be administered by IV as a bolus using preferably a power injector in a peripheral vein of the antecubital region (recommended). IMP injection will be followed by a 0.9% saline flush injection.
- The following information will be documented in the source document and recorded: contrast agent injection date and time, location of injection site, actual volume administered (documentation of difference with theoretical volume), actual injection rate, overdose (if any), number of IMP injected, injection method (power injector or manual), injection of saline flush (yes/no).
- The start time of contrast injection will be recorded.

Procedures to be followed after MRI examination:

The patient will stay at the trial site for between 30 and 75 minutes after the MRI examination is completed and the following procedures will be performed:

- Vital signs (systolic and diastolic BP and PR) will be obtained once between 30 and 75 minutes after the injection of contrast agent
- Assessment of AEs will be documented, including injection site reaction.
- Use/change of concomitant treatments during the visit will be documented.
- Safety follow-up visit (V5) needs to be scheduled 1 day post contrast agent injection.

8.1.5 For adult patients: 2nd Safety Visit – V5 – 1 day after 2nd Imaging Visit

- During this visit, the following assessments or tasks will be performed:
- Blood samples will be collected according to central laboratory manual.
- Vital Signs (systolic and diastolic BP, PR) will be recorded.
- Assessment of AEs will be documented, including injection-site reaction.
- Use/change of concomitant treatments / procedures / therapeutic measures will be documented.

8.1.6 Record of standard of truth based on histopathology results and other available clinical information

For patients who have undergone a biopsy or a surgery of an imaged lesion within 30 days after the last MRI examination, result of the histopathology is to be recorded. The date and type of sample collection (biopsy, surgery), as well as the size and location of the concerned lesion are to be recorded.

Final patient's diagnosis as per standard of truth if available will be recorded based on histopathology results if any and other clinical information.

8.2 Imaging Characteristics

8.2.1 Equipment

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

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

8.2.2 Imaging protocol

The same material and parameter setting for the same sequence should be used for unenhanced images and for each contrast-enhanced images in each patient, including contrast enhanced sequence acquisition timelines after contrast agent administration.

MRI machine manufacturer, type and field strength and power injector name used for the MRI examination will be collected.

The required sequences and parameters per patient for gadopiclenol and gadobutrol for adults should be as similar as possible. Depending on scanned organs/regions, different scanning protocol should be used. Core sequences for the majority organs are required per protocol are listed. Details on required sequence and parameters will be provided in the Imaging Manual.

8.2.2.1 CNS MRI

8.2.2.1.1 Brain MRI (axial orientation and whole brain are required):

- Unenhanced:
  - 2D T1-weighted SE/TSE images
  - 3D T1-weighted GRE images
  - 2D T2-FLAIR
  - T2-weighted TSE images
- Contrast-enhanced:
  - 2D T1-weighted SE/TSE images
  - 3D T1-weighted GRE images

8.2.2.1.2 Spinal cord MRI:

- Unenhanced:
  - T2-weighted TSE images (sagittal)
  - T1-weighted SE/TSE images (sagittal)

- Contrast-enhanced:
  T1-weighted SE/TSE (axial)
  T1-weighted SE/TSE (sagittal)

It is not allowed to add any sequence, other than the one described above, between contrast agent injection and axial 3D T1-weighted GRE for brain and sagittal T1-weighted SE/TSE for spinal cord.

8.2.2.2 Body MRI

8.2.2.2.1 Head and Neck MRI

- Unenhanced:
  - T2 Spin Echo/Fast Spin Echo
  - T1 Spin Echo
  - T1 Gradient Echo
- Contrast enhanced:
  - T1 Spin Echo
  - T1 Gradient Echo

8.2.2.2.2 Breast MRI

- Unenhanced:
  2D axial T1-weighted sequence
  2D axial T2-weighted sequence
  3D-T1 axial with fat saturation (at least one pre-injection)
- Contrast enhanced:
  Dynamic post contrast images (contrast-enhanced MRI): 3D axial T1 fat saturation weighted sequence after injection (minimum of 3 repetitions every 2 min.

8.2.2.2.3 Cardiac MRI (late gadolinium-enhancement only)

- Unenhanced:
  - Cine GRE
  - T1 mapping
- Contrast enhanced:
  - 2D or 3D IR T1-weighted GRE images (LGE)
  - T1 mapping

8.2.2.2.4 Liver MRI

- Unenhanced:
  Axial T2 with Fat Saturation
  Axial T1 GRE In/Out-of-Phase without Fat Saturation
  3D T1 with Fat Saturation
- Contrast enhanced:

Dynamic contrast-enhanced 3D-T1-weighted imaging with fat-saturated acquisitions: (precontrast, late arterial phase, portal venous phase (70-80 s post injection), and delayed phase (3 minutes post injection).

8.2.2.2.5 Pancreas MRI

- Unenhanced:
  Axial T2 with Fat Saturation
  DWI (Diffusion-Weighted)
  T1 GRE In/Out-of-Phase
  T1-GRE with Fat Saturation (Pre- injection)
- Contrast enhanced:
  Dynamic contrast-enhanced 3D-T1-weighted imaging with fat-saturated acquisitions: (Arterial phase (approx. 25 sec post injection), venous phase (approx. 60 sec post-injection), and delayed phase (approx. 3 minutes post injection)

8.2.2.2.6 Kidney MRI

- Unenhanced:
  T2 with Fat Saturation
  DWI (Diffusion-Weighted)
  T1 GRE In/Out-of-Phase
  T1-GRE with fat-saturated (Pre-injection)
- Contrast enhanced:
  Dynamic contrast-enhanced -T1-GRE with fat-saturated acquisitions: (Injection phase (approx. 25 sec post-injection), Follow-up of enhancement until at least 5 minutes post injection).

8.2.2.2.7 Prostate MRI

- Unenhanced:
  T2 weighted imaging
  T1-weighted imaging
  T1 weighted sequences (Pre-injection)
- Contrast enhanced:
  Dynamic T1 weighted sequences (Post Injection)

8.2.2.2.8 Female Pelvis MRI

- Unenhanced:
  T2 weighted and T2 weighted fat-suppressed
  Axial T1 weighted sequence
- Contrast enhanced:
  2D or 3D-T1 weighted sequence

8.2.2.2.9 Musculoskeletal system MRI

- Unenhanced:
  T2 weighted sequences with fat saturation
  Axial T1-weighted sequences SE/FSE
- Contrast enhanced:

Axial T1 weighted sequences SE/FSE

8.3 On-Site Reading of Images

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

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

Prediction of change in the patient management between the two Paired MRIs will be done on a global matched pairs fashion, blinded to the products.

8.4 Off-Site Reading of Images

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

Images will be evaluated by prospective evaluation of the blinded images in a centralized manner. All images will be sent to a core laboratory, which will prepare the images for evaluation. The file headers of all the images transmitted in DICOM format are to be edited to remove patient or center identification. For all images, any sequence information will be removed. A complete audit trail of any changes to the file headers will be maintained.

The blinded image evaluations will be performed by independent blinded radiologists assigned to CNS or any Body regions according to their expertise. For each region, 3 independent blinded radiologists will evaluate primary criteria per region.

The same 3 independent blinded radiologists will be involved to assess images on the global pairs fashion and 1 additional independent radiologist will perform lesion tracking.

An imaging eCRF will be used to ensure that the images and the diagnostic findings are properly aligned and to ensure that all data necessary for the trial purpose are documented by the independent blinded readers.

The methodology of the evaluations of blinded images is described in detail in the “Blinded Image Evaluation Charter”.

8.4.1 Manuals and Supplies

CO-SPONSORS (or the imaging core laboratory) will document the imaging tasks and procedures of the investigational site in an Imaging Manual. As defined in Section 8.2.2, the standardized image acquisition guidelines or imaging protocol will be provided to the sites as part of the Imaging Manual.

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

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

8.4.2 Site Qualification

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

8.4.3 Receipt and Tracking of Images

The investigational sites will submit anonymous images to the Imaging Core Laboratory in DICOM format. Images will be tracked in the database of the Imaging Core Laboratory.

8.4.4 Image Processing and Quality Check

Images received by the Imaging Core Laboratory as digital data will be translated from proprietary formats to a standard format. This data translation step enables capturing direct digital data. Patient identifiers are confirmed as removed, and the original digital data from the site is archived and stored.

The Imaging Core Laboratory will ensure that all imaging protocol requirements have been followed. If a problem with an image is identified (e.g.: inappropriate anatomical coverage, inconsistency of images parameters with the imaging protocol, poor quality images), the investigational site will be notified concerning the nature of the problems and the steps required for corrective action. The Imaging Core Laboratory will follow-up on all cases requiring remedial action by the investigational sites. CO-SPONSORS (or the Imaging Core Laboratory) may conduct site training for investigator sites with recurring image quality issues.

8.4.5 Independent Blinded Readers Training

A pool of independent readers (with specialty for the targeted organs/regions) with expertise in the interpretation of images from the trial diseases or imaging modality, with no participation in the trial and no affiliation with any institution where the trial will be conducted, will be selected for the off-site reading.

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

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

The term "independent" means that the readers involved in centralized review do not participate in image acquisition and images are read outside the image acquisition site.

8.4.6 Image Randomization

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

The patients within each batch will be presented based on randomized order without stratification into groups of patients.

Various modalities of images from the same patient will not be presented in the same batch and the Imaging Core Laboratory will ensure an appropriate wash-out period between the evaluations of images from two modalities (Pre and Paired images) and between two MR examinations for the same patient for adults, to minimize recall bias.

8.4.7 Blinded Assessment of Images

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

No communication on patient specific image findings will be allowed between the independent readers once the blinded reviews begin.

8.4.8 Inter & Intra-reader Variability Assessment

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

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

Intra-reader variability: individual readers will perform repeat image evaluations of 10% of cases randomly determined. The cases used for intra-reader variability assessment will be re-introduced randomly and re-read during the reading. To minimize recall bias, intra-reader variability will be assessed after an enough number of cases are reviewed and no sooner than two weeks from the original reviews of these patients. Results of the original reviews for these cases will not be available to the reader. Only the first evaluation of a given image set will be included in the efficacy analysis.

8.4.9 Lesion tracking/Matching

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

8.4.10 Image Archive and Final Deliverables

All imaging data will be maintained in a secure environment. The Imaging Core Laboratory will maintain a centralized image archive that will contain every imaging examination received from the clinical investigators for the trial. Measurements will also be stored so that these data may be audited if necessary. A copy of images transferred by the investigators to Imaging Core Laboratory will be transferred to CO-SPONSORS after database lock for archiving.

8.5 Non-Imaging Central procedures

8.5.1 Central laboratory – for adult patients only

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

All laboratory reports presenting results as listed in Section 7.2.3.5 must be promptly reviewed by the Investigator who will initial and date upon review. Change(s) in post-dose test values considered clinically significant, which would require either additional control or therapy, must be documented in the patient's source document. All change in values considered clinically significant by the Investigator will be reported as AEs and followed until recovery or stabilization of the values if irreversible (sequelae). Each lab reports are to be filled with the patient's source file.

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

The central laboratory manual will be provided to the investigators and will details the lab location, address, certifications and any other relevant information required by the investigators

8.5.2 ECG records and readings (only for pediatric population)

12-lead ECG machine and consumables will be supplied (and re-supplied if applicable) by ECGs Core Laboratory).

All materiel description, technical specification, specific requirements, user procedures will be provided to the site as part of the Site ECGs Manual.

ECGs Core Laboratory will document the ECGs tasks and obligations of the investigational site in the Site ECGs Manual (including ECGs transfers modalities).

The 12-lead ECGs will be sent to the ECG core laboratory continuously during the study for evaluation by an independent cardiologist according to the ECG reading charter. Parameters evaluated as listed in Section 7.2.3.3.

The ECG core laboratory will record whether the cardiologist is unable to evaluate the ECG. A comment field will be provided for the cardiologist to indicate factors that effected interpretation (e.g., lead reversal).

For ECGs a notable QTc change is defined as a QTc (Fridericia's or Bazett's) interval of greater than 450 ms for males and females. All such ECGs will be flagged by the core laboratory's cardiologist and require assessment for clinical relevance by the Investigator.

. All ECGs changes considered as abnormal and clinically significant by the investigator will be reported as AEs.

8.5.3 Blood sampling for PK (only for a subgroup of pediatric population)

A peripheral catheter will be placed for blood collection in the forearm or in the feet. As far as possible a venous line already in place for the current care (central or peripheral venous catheter) will be used for blood collection

The start of IMP administration is set as time point 0 (T0), and 3 blood samples will be collected per

patient (one sample will be obtained during the 10-60 minutes time window, the second sample will be obtained during the 2.0-4.0 hours' time window and the third sample will be obtained during the 6.0-8.0 hours' time window post-injection). For each patient, within each time window, the sampling time points will be allocated by IWRS, as per the Table 4 below, at the inclusion visit. Exact time of sample collection will be recorded.

Table 4: Time Window and Sampling Time Subgroups for PK Sampling

Time Window	Sampling time within Time Window (allocated by IWRS)
W1: 5 min to 60 min post-injection	**W1.1:** 5 min to < 25 min post-injection
	W1.2: 25 min to < 35 min post-injection
	W1.3: 35 min to < 45 min post-injection
	W1.4: 45 min to 60 min post-injection
W2: 2.0 hours to 4.0 hours post-injection	**W2.1:** 2.0 hours to < 2.5 hours post-injection
	W2.2: 2.5 hours to < 3.0 hours post-injection
	W2.3: 3.0 hours to < 3.5 hours post-injection
	W2.4: 3.5 hours to 4.0 hours post-injection
W3: 6.0 hours to 8.0 hours post-injection	**W3.1:** 6.0 hours to < 6.5 hours post-injection
	W3.2: 6.5 hours to < 7.0 hours post-injection
	W3.3: 7.0 hours to < 7.5 hours post-injection
	W3.4: 7.5 hours to 8.0 hours post-injection

Blood samples of at least 500µL each will be collected at each time point for analysis.

For gadopiclenol analysis, blood will be collected into sodium or lithium heparin tubes.

Plasma will be obtained within 30 minutes after blood collection by centrifugation at approximately 3000 rpm for 10 minutes and aliquots stored into polypropylene tubes at maximum temperature -15ºC or below for analysis (maximal time between end of centrifugation and freezing: < 2 hours). Plasma will be divided into two different aliquots for gadopiclenol analysis: 150 µL in the primary aliquot and at least 100 µL in the back-up aliquot.

The labelling of the tubes will include:

- Trial number
- Patient ID
- Time Window
- Theoretical and actual time of blood collection
- Plasma aliquot

The 2 aliquots (primary and back-up) for gadopiclenol determination will be sent on dry ice with temperature data logger to the central laboratory in separate shipments.

Details on PK samples handling will be provided to the investigational sites in a specific lab manual including recommendation that the overall trial-related blood loss will not exceed the limit of 0.9 mL/kg

body weight corresponding to 1% of total blood volume at a single time point and 2.4 mL/kg body weight (3% of the total blood volume during a period of four weeks).

The central laboratory will provide the sites with necessary PK kits to collect the blood samples and appropriate information regarding shipping of the samples to the central facilities.

9 SAFETY REPORTING

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

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

9.1 Adverse Event

9.1.1 Definition of Adverse Event

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

An AE can therefore be:

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

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

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

9.1.2 Collection and recording of Adverse Events

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

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

Details of collection, recording and reporting of Adverse Events – including SAEs/AESI/Special situation – and the responsibilities and workflow between the CO-SPONSORS GUERBET / Bracco and the CRO are described in the Safety Plan.

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

Periods and types of AEs to be reported	Screening	From 1st imaging visit to last follow-up visit	After end of participation
Not related non-serious AEs	X**	X	
Not related SAEs	X	X	
Adverse Event of Special Interest	X	X	
Related* AEs (serious or not)	X	X	X****
Pregnancy cases	NA	X	X***

* Related to the IMP and/or any protocol procedures including imaging procedures

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

*** See the period of collection described in section 9.3.2

**** If the investigator becomes aware of its occurrence.

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

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

9.1.3 Description of Adverse Events

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

- **Nature (diagnosis) of AE:** preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The investigator must report AE using standard medical terminology. The same terms should be used in the source documentation and in the eCRF.
- **Date and time of onset:** date and clock time of the AE start.
- **Intensity:**
    - Mild: the patient is aware of the sign or symptom, but it does not interfere with her/his usual daily activities and/or it is of no clinical consequence
    - Moderate: the AE interferes with the usual daily activities of the patient, or it is of some clinical consequence
    - Severe: the patient is unable to work normally or to carry out his/her usual daily activities, and/or AE is of definite clinical consequence.
- **Causal relationship to the Investigational Medicinal Product (IMP):**

- Related: the definition of adverse reaction (AR) implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.
- Not related: Applicable when no IMP has been administered (pre-administration period) or when no causal relationship exists between the trial drug and the event, but an obvious alternative cause exists (e.g., the patient's underlying medical condition or concomitant therapy).

- **Causal relationship to a trial procedure (blood test, imaging procedure itself, etc…):**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the procedure. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no procedure was performed yet or when no causal relationship exists between the trial procedure and the event, but an obvious alternative cause exists (e.g., the patients underlying medical condition or concomitant therapy).
- **Outcome:**
  - Recovered/resolved: the AE is no longer present at any intensity or return to baseline intensity (for pre-existing disorders) or values for biological data.
  - Recovered/resolved with sequelae: the AE is resolved but residual effects are still present (to be specified on the AE form).
  - Not recovered/not resolved: the AE is still present at the last contact with the patient.
  - Fatal: this AE caused or directly contributed to the patient's death.
- **Date of the event end (or consolidation):**
  - This date is the date when the event has come to its ends or to its initial intensity (for the events that had been an aggravation of a pre-existing disorder).
  - If the AE is still ongoing by the time of end of trial follow-up for the patient (i.e., last trial visit), the patient should be followed-up until AE resolution or a justification should be provided by the Investigator (i.e., chronic disease) in the medical file.
- **Action taken with regard to administration of the IMP:**
  - No action: for AE occurring during the pre-treatment/procedure after the post-treatment/procedure period, or if the IMP dosing/administration would not change despite the occurrence of the AE
  - IMP interrupted: the IMP administration is interrupted during the administration (e. g. extravasation…) or the patient is withdrawn from any other IMP administration planned during the trial but without known contra-indication to the drug (e.g., AE leading to trial discontinuation before the 2nd MRI)
  - IMP definitively discontinued: the event leads to a definite contra-indication to the drug (e.g., confirmed hypersensitivity…).
- **Other action taken:**
  - IMP unblinding (for adult cohort only)
  - AE-targeted medication: the patient took a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the eCRF ("concomitant medication" section).

- Other AE-targeted action: therapeutic measures other than corrective drug administration (e.g., ice, heating pad, brace, cast…) or patient underwent a procedure (surgery, physiotherapy, additional laboratory test…) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the eCRF ("procedures/therapeutic measures" section).
- Trial discontinuation: the AE leads to a trial discontinuation,

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

9.2 Serious Adverse Event

9.2.1 Definition of Serious Adverse Event

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

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

- Important medical event: medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
- Life-threatening in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Hospitalization refers to an admission and overnight stay at the hospital due to the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

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

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

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

- Any hospitalization that had been planned before the trial and that will take place during the trial, provided there is no aggravation of the disease to which it is related.

- Hospitalizations, which are not associated to an adverse event (such as hospitalization for check-up).

No anticipated SAE is defined in this protocol as patient population under trial is suffering from abnormalities of various regions of the body but not from a specific pathology therefore no anticipated SAE has been identified.

9.2.2 Reporting Serious Adverse Events (SAE)

All SAEs **must be reported immediately and no more than 24 hours** by the investigator to GUERBET. Therefore, the investigator must immediately forward to GUERBET Pharmacovigilance department a duly completed report form for SAE, AESI or pregnancy (F001406) provided by GUERBET with trial documents, even if it is obvious that more data will be needed in order to draw any conclusion:

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

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

+ 33 (0)1 45 91 50 00.

Due to the CO-SPONSOR nature of the trial, Bracco will be informed by GUERBET of any SAE reported by an investigator.

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

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

- Patient's details including age, sex, and patient's trial identification number
- Patient's medical history relevant to the assessment of the event
- Type of event by reporting a diagnosis or if not available, symptoms
- Date and time to onset of the event
- End date of the event (will be reported in a follow-up report if the event is still ongoing at the time of initial notification)
- Date and time of investigational drug administration,
- Seriousness criterion
- Causal relationship to the investigational drug or procedure (mandatory)
- Outcome at the time of reporting

If the investigator is aware of any new relevant information concerning a SAE (e.g.: outcome or any information that can have an impact on the assessment of the seriousness or the causal relationship between the SAE and the IMP), he has to send immediately to GUERBET Pharmacovigilance department the report form for SAE, AESI or pregnancy duly completed (F001406).

To comply with current regulations as well as for comprehensive assessment purposes, additional information (e.g., autopsy results, biological values…) or clarifications may be required by GUERBET in a timely fashion to ensure accurate follow-up and assessment of each case and should be transmitted, anonymized, with a specific form (F018362) as soon as they are available.

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

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

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

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

9.3 Special Situations

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

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

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

9.3.2 Pregnancy

Any participating patient who becomes pregnant during the trial participation should inform immediately the investigational site. The female patient should immediately withdraw from the trial and must not receive any IMP.

Any pregnancy (with or without an Adverse Event) of a woman participating in the trial that is discovered after the ICF signature must be reported to GUERBET Pharmacovigilance *via* the report form for SAE, AESI or pregnancy (F001406) (see section 9.2.2) unless the conception date is before the first IMP administration or over one week after an IMP administration. In this case, there is no need to report the pregnancy to GUERBET except in case of noxious effect related to the trial drug according to investigator's opinion.

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

Specific forms "history and start of pregnancy" (F006030) and "course and outcome of pregnancy" (F006033) will be provided to the investigational sites by GUERBET Pharmacovigilance department.

These forms will be used to collect information on the medical history of the pregnant woman and any risk factor of pregnancy complication, and on the follow-up and outcome of the pregnancy.

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

9.3.3 Adverse Events of Special Interest

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

For GUERBET, the transmission of an AESI to the GUERBET Pharmacovigilance Department respects the same time frame as an SAE and should be reported using the report form for SAE, AESI or pregnancy (F001406).

The AESI for this protocol is the following: Nephrogenic Systemic Fibrosis (NSF). NSF is primarily characterized by thickening of the skin and subcutaneous tissue in addition to systemic manifestations.

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

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

9.4 Other Important Safety Issue

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

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

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

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

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

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

- Premature discontinuation of the patient

9.5 Unblinding Procedures

The investigator may, under exceptional circumstances unblind the individual trial treatment group for adult patients if he/she considers that this procedure is relevant to the safety of the trial. Individual trial treatment unblinding is described in section 5.3.3. Information that unblinding has been performed by the investigator must be documented in the patient medical file, in the clinical eCRF and in the report form for SAE, AESI or pregnancy sent to GUERBET Pharmacovigilance Department, if applicable.

Suspected Unexpected Serious Adverse Reaction (SUSARs) will be unblinded by GUERBET Pharmacovigilance Department for regulatory reporting purposes; however, these SUSARs will remain blinded to the investigator and to GUERBET personnel responsible for trial management, data analysis, and interpretation of results at the trial's conclusion.

10 SCREEN FAILURE AND PREMATURE DISCONTINUATION

10.1 Screen Failure

For adult patients, screen failed patients are defined as patients who consent to participate in the clinical trial but are not subsequently randomized for this trial, a patient who has signed ICF can be re-screened if he/she has not been randomized.
For the children, screen failed patients are defined as patients for whom ICF has been signed by parents but to whom subsequently gadopiclenol is not attributed. For data to be collected for screen failed patients please refer to section 14.3.2.

10.2 Premature Discontinuation of the Trial per CO-SPONSORS Decision

CO-SPONSORS reserve the right to discontinue the trial at any time for medical, administrative, or other reasons.
CO-SPONSORS will inform the relevant authorities in each country, the ethics committees, the trial site investigators, pharmacists, and hospital authorities according to the regulatory texts in force.

10.3 Premature Discontinuation of the Patient

Premature discontinued patients are defined as patients who consent to participate in the clinical trial and are discontinued from the trial after randomization (or gadopiclenol attribution for pediatric patients).

Patients who do not have the record of a patients' diagnosis as standard of truth are not considered as prematurely discontinued.

For data collected for premature discontinued patients please refer to section 14.3.2.

10.4 Reasons for Patient's Screening Failure and Premature Discontinuation

Criteria for screen failure and premature discontinuation of patients:

- Inclusion criteria not met / Non-inclusion criteria met.
- Adverse Event (according to the investigator's judgement).

- Adverse Event of Special Interest (AESI).
- Withdrawal of patient's or parent's/legal guardian's consent:
    - If the patient withdraws consent for disclosure of future information, CO-SPONSORS may retain and continue to use any data collected before such a withdrawal of consent.
    - If a patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site's records.
- Patient lost to follow-up (date of last contact will be documented in the medical file and the eCRF). Any effort will be undertaken to know the reason for this loss to follow-up and/or to exclude any adverse reaction as this reason. This will be documented in the patient's medical file.
- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the trial.
- At the discretion of the investigator if the patient safety or well-being is not compatible with trial continuation.
- Other reason (to be specified)
- Screen failure or premature discontinuation of patient is related to Covid-19, Yes/ No.

10.5 Enrolment of Additional Patients

Patients prematurely discontinuing the trial will not be replaced. In the event of premature discontinuation, patients will receive adequate follow-up from on-site investigators.

11 STATISTICAL CONSIDERATIONS

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

11.1 Statistical Method

Primary analysis: non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria in adult patients.

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

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

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

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

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

11.2 Sample Size

Number of patients for the 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%).

- Sample size hypothesis:

The standard deviation on lesion visualization criteria for gadopiclenol is estimated based on 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 considering 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 or each co-primary criterion. An enrollment of 168 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin, assuming 85% 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 15%, an enrollment of 200 patients is necessary to meet primary objective for adult patients.

Considering that the non-matching lesions was mainly the results of reading variability in the selection of lesions in the previous phase III studies, up to the 10 largest and most enhancing lesions will be evaluated for the co-primary criteria. In that case, the number of non-matching lesions is likely to be

very reduced and planned enrollment is considered as enough to show non inferiority in those two sensitivity analyses.

Number of patients for the pediatric cohort:

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 38 children in the gadopiclenol group will have 85% 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.

Sample size for population of the PK analysis is not based on statistical consideration and has been calculated taking into consideration limitation and difficulties to collect many samples without interfering with patient care and duration of hospital stay. Sparse sampling strategy used for PK sampling in this trial reduces considerably the burden of blood sampling for each patient and was implemented also in other trials performed by GUERBET in PK analyses in children. This, PK analyses performed even in a small number of Japanese pediatric patients will allow assessment of gadopiclenol pharmacokinetics in plasma in children.

Based on these considerations, CO-SPONSORS estimated that 6 patients per age group, i.e., 24 patients, in the population of the PK analysis will be sufficient to inform gadopiclenol pharmacokinetics in plasma in Japanese children. In case age groups are not or partially completed, the impact of a reduced sample size on the precision of parameter estimates will not be an issue since the available data will be fitted into a model based on a large sample size and including Japanese and non-Japanese adult participants as well as non-Japanese pediatric participants. A simulation approach based on this

established model enriched with available Japanese pediatric data, will be used to simulate the missing patients, if any.

11.3 Planned Analysis

The separate statistical analysis for adults and pediatric cohorts can be considered in case the time lapse between the end of enrollment in both cohorts is more than six months.

11.3.1 Disposition of patients

Number of patients undergoing each visit will be presented separately for adult and pediatric cohorts. For adult patients, this will be presented by sequences (gadopiclenol-gadobutrol / gadobutrol-gadopiclenol) and overall. For pediatric patients, this will be presented overall.

The overall disposition will be presented separately for adult and pediatric cohorts. For adult patients, this will be presented by sequences (gadopiclenol-gadobutrol / gadobutrol-gadopiclenol), by body region and overall. For pediatric patients, this will be presented by age group and overall by population (CNS and Body) and globally.

The reason of screen failure will be presented overall and the reason of premature discontinuation will be presented by sequences and overall for adult cohort. The reason of screen failure will be presented by age group and overall and the reason of premature discontinuation will be presented by age group, by population and overall for pediatric cohort. See section 10 for screen failure and premature discontinuation definition.

Number of patients by site will be presented overall for both cohorts.

11.3.2 Data Sets Analyzed

The patient sets for this trial are defined below:

- 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 having signed the inform consent form
- 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 at least one 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 enhanced MRI exam
- The Per-Protocol Set adults (PPSa) will include all patients from the FASa who have no major protocol deviations

11.3.3 Protocol Deviations

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

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

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

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

- Patient not presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one region among CNS, thorax (e.g. breast), abdomen (e.g. liver, pancreas, and kidney), pelvis (e.g. uterus, ovary, and prostate), musculoskeletal (e.g. extremities)
- Imaging protocol not respected with major impact on primary criterion
- Informed consent not signed
- IMP not injected

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

Major deviations will be presented only for adult patients. Non-major deviations will be presented apart, for adult and pediatric patients separately; for adult patients, by sequences and overall and for pediatric patients, by age group, population and overall.

11.3.4 Demographics and Baseline Characteristics

Demographic parameters are age, sex, race, childbearing potential, body weight, height, and body mass index (BMI). Baseline characteristics are the patient's history (including the medical history and the disease requiring the trial MRIs) and the concomitant treatments.
Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height, and BMI. Frequency and percentages will be calculated for sex, patient’s history characteristics and concomitant treatments.
Patient's medical history will be coded using the MedDRA dictionary and tabulated by body system, preferred term, and status (concomitant or not).
Patient's concomitant treatments will be coded using the Anatomical Therapeutic Chemical (ATC) Drug dictionary and tabulated by ATC code.
Demographics and baseline characteristics will be displayed for adult and pediatric patients separately and for adults by sequences and overall.

Summary of histopathology used for standard of truth will be presented for adult patients with evaluation available.

11.3.5 Compliance

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

The absolute (mL) and relative (%) differences between theoretical and actual volumes of trial product will be tabulated for adult and pediatric patients separately and for adults by contrast agent group.

11.3.6 Population PK analysis

The population PK analysis will be performed on the PK set using a dedicated software modelling and including pharmacokinetic models library.

The structural model describing the gadopiclenol concentrations profile as a function of time and amount of product injected will be first determined. Structural PK model parameters will enter the model either as fixed or random effects (when supporting a between-patient variability).

Covariates potentially influencing the PK of gadopiclenol will be tested using a backward sequential approach in order to prevent inflation of the type I error over the number of statistical tests.

Quality of the model will be assessed using goodness of fit plots and an internal validation will be performed using visual predictive checks.

Gadopiclenol plasma concentrations below the limit of quantification will be considered as missing, unless their proportion represent more than 15% of the total concentrations. In that case, alternative methods, such as left-censoring, will be considered for their contribution to the likelihood.

Empirical Bayes estimates (EBEs) of PK parameters (basically clearance and volume of distribution) will be obtained from the final model and summarized per age group and overall. In addition, the following parameters will be derived from the EBEs, depending on the structural model retained for gadopiclenol:

- Area Under the Curve,
- Elimination half-life,
- Total clearance,
- Volume of distribution.

In addition, gadopiclenol plasma concentrations at 10, 20 and 30 minutes post-injection will be simulated from the final model and their distribution will be summarized using box-plots and descriptive statistics by cohort, age group and overall.

All methods to be applied for the population modelling will be fully detailed in a dedicated analysis plan.

11.3.7 Efficacy Analysis

11.3.7.1 Primary analyses

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

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

11.3.7.2 Sensitivity analyses

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualization co-primary criteria in adult patients 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 will be considered for this analysis. Score for non-matching lesions will be imputed to the worst that is to say to a score equal to 1. Therefore, there will not be missing data in the modelization.

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

Same analysis as the primary analysis will be conducted. All lesions including matching and non-matching will be considered for this analysis. Score for non-matching lesions will be imputed to the worst that is to say to a score equal to 1. Therefore, there will not be missing data in the modelization. The imputation is done in the way to maximize the difference between gadopiclenol and gadobutrol to show the robustness of the non-inferiority.

11.3.7.3 Secondary analyses

Additional analysis of the co-primary criteria

Superiority of Paired images versus Pre images of gadopiclenol MR examination regarding lesion visualization at patient level.

The difference "Paired" – "Pre" for each of 3 co-primary criteria will be analyzed using paired t-tests on the FAS for both cohorts. Results will be presented per off-site readers. This analysis will be performed with the following conventions:

- in adult patients on matching lesions and non-matching lesions with imputation
- in pediatric patients on matching lesions and non-matching lesions with imputation

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.

Supportive analyses of the primary and sensitivity analyses
The non-inferiority analyses (primary) will be repeated on 3 various combinations of radiologists using the PPS.

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

Subgroup analysis for adult patients
Non-inferiority analysis will be conducted using the same linear model and data as primary analysis with organ, region (CNS, body regions), demographic characteristic as additional factors.

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

Inter- reader variability
Inter-reader variability will be evaluated using the PPSa for the adult cohort and the FASp for pediatric cohort.

Secondary criteria analyses

All analyses of the **s**econdary criteria will be done using the FAS, for adult and pediatric cohorts separately; in adult patients by GBCA and in pediatric patients by regions and overall, except otherwise specified.

Technical adequacy of images
Technical adequacy, assessment of overall contrast quality and assessable status of images will be tabulated, off-site and on-site reader's outcomes will be separately analyzed.

Size of lesions
The size of up to 10 lesions per patient will be tabulated, off-site and on-site reader's outcomes will be separately analyzed.

Location of lesions
The location of up to 10 lesions by patient will be only listed.

Diagnostic confidence

The diagnosis of each lesion according to off-site readers and on-site radiologists will be tabulated, off-site and on site reader's outcomes will be separately analyzed.
Diagnostic confidence will be tabulated, off-site and on-site reader's outcomes will be separately analyzed.

Diagnostic value evaluation
Patient's diagnosis as per standard of truth will be presented. Both GBCA (gadopiclenol and gadobutrol) imaging diagnosis will be presented by reader displaying number and frequency true positive and true negative patients according to standard of truth.

The following parameters will be calculated:

Sensitivity: the number of true positive patients divided by all positive patients according to standard of truth

Specificity: the number of true negative patients divided by all negative patients according to standard of truth

Accuracy: the number of true positive patients plus the number of true negative patients divided by all patients with standard of truth

Positive predictive value: the number of true positive patients divided by all positive patients according to GBCA imaging

Negative predictive value: the number of true negative patients divided by all negative patients according to GBCA imaging

Comparison between gadopiclenol and gadobutrol
The sensitivity of the two GBCA will be compared using a logistic regression with repeated measures modelling the probability that a patient is malignant as a function of the GBCA administered.
The specificity of the two GBCA will be compared using a logistic regression with repeated measures modelling the probability that a patient is not malignant as a function of the GBCA administered.

Patient treatment plan:
The patient treatment plan will be assessed by on-site radiologists and impact will be only listed.

Percentage enhancement (E%) of lesion
E% is calculated by the 3 independent off-site readers (see section 7.2.3).

For each reader, E% will be tabulated. Differences between contrast agents will be tested using a Student's t-test for adult cohort.

Lesion to Background Ratio (LBR)
LBR is calculated by the 3 independent off-site readers (see section 7.2.3).

For each reader, LBR will be tabulated. Differences between contrast agents will be tested using a Student's t-test for adult cohort.

Contrast to Noise Ratio (CNR)
CNR is calculated by the 3 independent off-site readers only for patients referred for CNS MRI (see section 7.2.3).

For each reader, CNR will be tabulated. Differences between contrast agents will be tested using a Student's t-test.

Overall diagnostic preference

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

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

Number of lesions

For adult cohort, the number of lesions per patient will be tabulated by contrast agent groups; lesions detected on gadopiclenol MR images will be cross tabulated with lesions detected on gadobutrol MR images. Off-site and on-site reader's outcomes will be separately analyzed.

For pediatric cohort, the number of lesions per patient will be tabulated by MRI modalities; lesions detected on unenhanced MR images will be cross tabulated with lesions detected on gadopiclenol MR images. Off-site and on-site reader's outcomes will be separately analyzed.

All details of the evaluation methods and presentation of results will be described in the Statistical Analyses Plan (SAP)

11.3.8 Adverse Event

A summary of all AEs will be presented using the Screened Patient Set (SPS) to catch AEs of patients who did not receive trial drug as well. The table will be presented overall and per group of age for the pediatric cohort and overall for the adult cohort with the following variables:

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) overall and by seriousness criteria.
- AESIs,
- AEs with causal relationship to a trial procedure.
- AEs according to intensity,
- AEs according to the outcome,
- AEs requiring a concomitant drug/procedure,
- AEs leading to trial premature discontinuation.
- AEs leading to IMP interruption

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

Same summary table will be provided for AE occurring before IMP administration and for screen fail patients.

A summary table will be displayed by contrast agent group and overall for the adult cohort and per group of age for the pediatric cohort for Treatment Emergent AEs (TEAEs) using the Safety Set. The following variables will be presented in addition to those presented in the all-AE summary table:

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

The same table will be presented by indication for both adult and pediatric cohorts.

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

The same table will be presented by indication for both adult and pediatric cohorts.

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

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

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

11.3.9 Clinical Laboratory data

Clinical laboratory data analysis will be done using the Safety Set, for adult and pediatric cohorts separately. In adult patients, data will be tabulated by GBCA and in pediatric patients by age group and overall, except otherwise specified.

The statistical analysis will present results in standard international units. Laboratory data will be analyzed quantitatively and qualitatively.
Qualitative analyses will be done via comparison of laboratory data to their respective reference ranges and according to their clinical significance. Quantitative analyses will be done by tabulating raw data and change from baseline.

11.3.10 Other safety observations

Other safety observations analysis will be done using the Safety Set for adult and pediatric cohorts separately. In adult patients, data will be tabulated by GBCA and in pediatric patients, by age group and overall, except otherwise specified.

Extent of exposure

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

Vital signs

Vital signs will be analyzed quantitatively. Analyses will be done by tabulating raw data and change from baseline.

ECG data

ECG data will be analyzed quantitatively. Analyses will be done by tabulating raw data and change from baseline.

11.4 Specific Statistical Analytical considerations

11.4.1 Adjustments for Covariates

As no factor has been identified as having a large impact on the primary co-criteria, no covariates are added in the efficacy models for adult nor pediatric population.

11.4.2 Handling of Dropouts or Missing Data

No imputation will be performed in this trial.

11.4.3 Interim Analyses

No interim analysis is planned

11.4.4 Multicentre Trial

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

11.4.5 Multiple Comparisons/Multiplicity

Primary objective (non-inferiority of gadopiclenol compared to gadobutrol for adult patients) will be considered achieved only if the null hypothesis is rejected for the 3 co-primary criteria simultaneously for at least two readers out of three. Each reader will be analyzed separately.

Other analyses are exploratory.

11.4.6 Use of an "Efficacy Subset" of patients

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

11.4.7 Examination of Subgroups

Co-primary criteria descriptive statistics will be provided by organ and regions.

Sensitivity analyses of the non-inferiority analysis for adult patients will be conducted using the same linear model with region as additional factors.

The robustness of GBCA effect across different regions and/or organs will be discussed with following information:

- Descriptive summary statistics for each region and/or organs
- Effect estimations for each region and/or organ with the associated 95% two-sided CI. Overlapping of all regions and/or organs CI estimates with the confidence interval for the overall effect will be checked.

Graphical visualization of the regions and/or organs with a Forest plot for each region and/or organ of the LS Means difference and also the LS Means Ratio.

12 TRIAL COMMITTEES

An Independent Data Monitoring Committee (IDMC) will not be set up for this trial/study considering the following aspects: product characteristics and available safety data, study population, short study duration and single injection.

- Product characteristics (macrocyclic GBCA - distribution in the extracellular water compartment, no protein binding, no metabolism, and rapid urinary excretion - similar PK profile between non-Japanese adults and children (2-17 yo) population, similar profile between non-Japanese and Japanese healthy volunteers
- Pathology and indication: diagnostic indication in CNS and body are the same as in previous clinical trials in adults and children
- Trial endpoints: no interim analysis is planned in this trial
- Trial duration: short duration of participation for a patient with a single injection of gadopiclenol in half-dosage gadolinium compared to other GBCA
- Knowledge available on the gadopiclenol: safety profile well described based on previous clinical trials in 1065 exposed to gadopiclenol including 80 children aged 2 to 17 years
- Trial design does not present any particular complexity and is open labeled

For all these reasons, an IDMC (Independent Data Monitoring Committee) has not been established for the trial. Investigational sites and the Co-Sponsors will be responsible to ensure the trial/study discontinuation rules are applied.

A prudent approach has been adopted in inclusion of younger pediatric population. Trial Safety Review Board (TSRB) will be established mainly for the careful review of the safety data of first 50 adult patients and the first 10 children including at least 3 young patients (aged from 2 to 6 years), as well as GDX-44-015 study data in non-Japanese pediatric patients aged < 2 years old in order to take a decision to start the inclusion in the group of patients aged from birth to 23 months inclusive. TSRB will perform a risk/benefit assessment and monitoring the overall conduct of the clinical trial in children cohort.

Review of safety data will be based on disposition demography and other baseline characteristics as well as all safety parameters (AE, laboratory data and other safety observation such as vital signs and ECG).

The TSRB is composed as following: an identified medical expert in pediatric radiology and CO-SPONSORS team (drug safety physician, medical expert, clinical project manager and ad-hoc team members).

The role and responsibilities of the TSRB will be described in a separate document (TSRB Plan) that will be written before first TSRB Meeting.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 References

The trial will be conducted in accordance with the following regulatory / guidance texts:

- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, June 1964, and amended in: October 1975 (Tokyo), October 1983 (Venice), September 1989 (Hong Kong), October 1996 (Somerset West), Scotland, October 2000 (Edinburgh), 2002 (Washington), 2004 (Tokyo), October 2008 (Seoul), October 2013 (Fortaleza)

- Ministerial Ordinance on Good Clinical Practice for Drugs1: Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997 (As last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 161 of December 28, 2012), J-GCP.
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 19 November 2016
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A Current Step 4 version dated 27 October 1994
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials E8 Current Step 4 version dated 17 July 1997
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1) Current Step 4 version dated 5 February 1998
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Investigation of Medicinal Products in the Pediatric Population E11 Current Step 4 version dated 20 July 2000 and E11 (R1) Addendum dated 20 July 2017
- Regulation (EU) 2016/679 Of The European Parliament And Of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 11 on Electronic Records; Electronic Signatures
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals
- Any applicable local regulation

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

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

In case of modifications to the trial protocol, patient informed consent form or any other written information provided to the patients, or to any trial procedure; the modified documents will be submitted to IRB/IEC and Regulatory/Competent Authority opinions. Modifications may be implemented when the final approval and authorization are available.

In case of an emergency situation when the patients' safety may be at risk, CO-SPONSORS may implement emergency safety measures prior to obtaining IRB/IEC approval and Regulatory/Competent Authority opinion. In parallel to implementing these measures, CO-SPONSORS will immediately notify the concerned IRB/IEC and Regulatory/Competent Authorities of such implementation.

The documentation related to the approvals and authorizations must be filed in the trial Master File at CO-SPONSORS and at the investigational sites in their respective Investigational Site File (ISF).

Notification of Serious Adverse Events/Reactions to IRB/IEC and Regulatory/Competent Authority will be made according to the national requirements. Safety reporting is described in SAFETY REPORTING of the present protocol.

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

13.3 Patient Informed Consent (J-GCP Article 7, Section 4; Article 50～55)

13.3.1 Patient Information and Patient Informed Consent – Adult and pediatric Patients

Prior to participation, all adult patients and all patients' parent(s) or legal guardian (where applicable) of pediatric patients, must confirm their free and voluntary willingness to participate in the trial. This confirmation is obtained in writing after having received a full oral and written explanation on the trial:

- Aims, methodology and duration of the trial;
- Potential benefits, foreseeable risks and inconveniencies related to the trial;
- Rights and responsibilities of adult patients and patients' parent(s) or legal guardian (where applicable) of pediatric patients, with particular emphasis on the right to refuse trial participation or to withdraw consent to participation at any time without consequences or penalties;
- Information on IMP and its administration;
- Contact details of persons dedicated to the trial at the investigational site.

Pediatric patients should participate in the informed consent process together with the parent(s) or legal guardian (where applicable), in a way that is appropriate to his or her age and maturity.

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

Adult patients and patients' parent(s) or legal guardian (where applicable) of pediatric patients may consent to participate after having received all necessary information and all satisfactory answers to their questions. Their consent must be confirmed in writing by dating and signing the informed consent form(s) approved by the corresponding IRB/IEC.

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

The information of adult patients and patients' parent(s) or legal guardian (where applicable) of pediatric patients may only be conducted by qualified investigational site personnel, whose involvement and responsibility for patient information has been fully documented and approved by the Principal Investigator.

The Principal Investigator must ensure that local applicable regulations/requirements are fully observed by the staff under her/his responsibility.

In case of modifications of the adult patients and patients' parent(s) or legal guardian (where applicable) of pediatric patients informed consent or of any other document to be provided to them, the IRB/IEC approval must be obtained prior to implementing the new document(s). Adult patients and patients' parent(s) or legal guardian (where applicable) who already consented may be asked to confirm their willingness to continue participating in writing. In any case, the same information and consent process as described above must be followed.

13.3.2 Pediatric Patients Participating in PK Analyses

Information trial procedures related to PK analyses is included in the PATIENT'S PARENT(S) OR LEGAL GUARDIAN INFORMATION AND CONSENT FORM.

Prior to participation, all patients parent(s) or legal guardian (where applicable) must confirm their free and voluntary willingness to involve their child in the PK analyses cohort. This confirmation is obtained in writing after having received a full oral and written explanation on the trial and is marked in the Informed Consent Form accordingly. Such involvement must be fully documented in the patient's medical records and the informed consent.

13.3.3 Patient Information and Patient Informed Consent – Child reaching the age of Majority

If a child reaches the age of majority while participating in the trial, the following procedure is foreseen:

- The patient is fully informed of the trial and its procedures as described in section 13.3.1.
- The patient receives the written Patient (at age of majority) Information and Consent Form, and the investigational site proposes him/her to give the written consent to continue study participation.

The trial procedures are continued with the patient as planned before reaching the age of majority. However, the patient's written informed consent is needed to continue documenting any trial related data into the eCRF. If he/she refuses, no data of subsequent examinations (e.g. standard of truth) will be collected.

13.4 Trial Records and Archiving (J-GCP Article 7, Paragraph 10)

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

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

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

At the end of the trial, investigational sites must ensure the ISF will be archived in an appropriate way that allows timely access and proper retention of documents. All documentation relating to this Trial should be retained for 3 years after the last approval or for 3 years after discontinuation or termination of clinical trial, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

14 QUALITY CONTROL / QUALITY ASSURANCE

14.1 Direct Access to Source Data/Documents (J-GCP Article 7, Paragraph 9)

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

The investigator must guarantee the safety of the trial data in the medical files by implementing security measures to prevent unauthorised access to the data.

The investigator undertakes, in accordance with the regulation in force, to make anonymous any patient data before collection by CO-SPONSORS. Especially the name and address of the patients will be deleted from any medium such as eCRF, document for biological results, X-Ray films or digital supports.

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

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

14.2 Clinical Monitoring

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

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

14.3 Clinical Data Handling

14.3.1 Data Reported in the eCRF

The eCRF will allow recording of all the data required by the protocol except detailed central laboratory results (only adults patients), central ECG assessment and blinded imaging assessment performed by independent readers entered in imaging eCRF.

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

The investigator must attest:

- The authenticity of the data collected in the eCRF;
- The consistency between the data in the eCRF and those in the source documents, with the exception of those data recorded directly in the eCRF and considered as source data (on-site rading data could be recorded directly on the eCRF (i.e., no prior written or electronic record of data), and to be considered to be source data.

14.3.2 Data Reported in the eCRF according to Patient Status

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

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

For patients discontinued from the trial after randomization, all data available at the time of discontinuation will be reported in the medical file and the eCRF (e.g.: inclusion data, safety data, administration data, imaging data, reason for premature discontinuation…). The investigator must make every effort to collect and record all follow-up safety information (i.e., adverse events, injection-site reaction, as appropriate), unless the patient withdraws consent for further data collection/participation for/in the trial.

14.3.3 Data Management System

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

Data processing and control will be closely managed by CO-SPONSORS's representative.

14.4 Audits and Inspections

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

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

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

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

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

15 PUBLICATIONS RULES

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

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

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

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

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

All written or oral papers and publications must have the joint agreement of the investigator and CO-SPONSORS.

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

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

In addition, and according to local regulations, the trial/study may be registered on local regulatory or public databases by CO-SPONSORS.

No direct registration of trial/study information will be made by the investigator on any database without prior agreement of CO-SPONSORS.

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17 COMPANY LIABILITY INSURANCE

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

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

However, CO-SPONSORS and its insurer reject all liability in the following cases, which are merely indicative and not exhaustive:

- An accident due to a cause other than the investigational medicinal product administered,
- An accident occurring during use of the investigational medicinal product differently from the instructions given in the trial protocol,

An accident occurring for a patient whose consent to participation was not adequately collected.

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Identifiant d'enveloppe: [redacted]

État: Complétée

Objet: Complétez avec Docusign : GDX-44-014 – GDX-101 - Protocol 22 Oct 2024 (4).docx

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Horodatage de l'enveloppe: Activé

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[redacted] Biostatistician Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	[redacted] Sélection d'une signature : Style présélectionné ID de signature: [redacted] Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'ai examiné ce document	Envoyée: 24-oct.-2024 | 04:33 Consultée: 24-oct.-2024 | 05:04 Signée: 24-oct.-2024 | 05:05

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Nom de la société: GxP 2

Divulgation relative aux Signatures et aux Dossiers électroniques:

Accepté: 24-oct.-2024 | 02:31

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[redacted] Latam Medical Director Guerbet Niveau de sécurité: E-mail, Authentification de compte (obligatoire), Connexion avec SSO	[redacted] Sélection d'une signature : Style présélectionné ID de signature: [redacted] Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): Aprovo este documento	Envoyée: 24-oct.-2024 | 04:33 Consultée: 24-oct.-2024 | 06:40 Signée: 24-oct.-2024 | 07:10
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[redacted] Bracco Diagnostics Inc. Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	[redacted] Sélection d'une signature : Style présélectionné ID de signature: [redacted] En utilisant l'adresse [redacted] Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): I approve this document	Envoyée: 24-oct.-2024 | 04:33 Renvoyé: 25-oct.-2024 | 06:10 Consultée: 25-oct.-2024 | 06:19 Signée: 25-oct.-2024 | 06:20
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Enveloppe envoyée	Haché/crypté	24-oct.-2024 | 04:33
Livraison certifiée	Sécurité vérifiée	25-oct.-2024 | 05:59
Signature complétée	Sécurité vérifiée	25-oct.-2024 | 05:59
Complétée	Sécurité vérifiée	25-oct.-2024 | 06:20
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