Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI

Phase II Clinical Trial

EudraCT No.: 2021-003825-31

IND No.: 123673

COORDINATING INVESTIGATOR

PPD

PPD

PPD

PPD

SPONSOR

GUERBET, B.P. 57400, 95943 Roissy CdG Cedex, FRANCE

GUERBET MEDICAL EXPERT

PPD

PPD

PPD

GUERBET PHARMACOVIGILANCE

E-mail: pharmacovigilance.headquarters@guerbet.com

Ref. No.: 4_23_00069

PROTOCOL SYNOPSIS

Trial Title: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Trial	
Trial Product: G03277.100	Active Ingredient(s): gadopiclenol
EudraCT No.: 2021-003825-31	IND No.: 123673
Potential Participating countries (Potential Number of sites): Worldwide trial involving approximately 15-20 centers in 4 regions/countries in Europe and USA.	

Trial Objectives

Primary objective:

To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection of 0.05 mmol/kg body weight (BW) in pediatric population aged up to 23 months (inclusive) scheduled for a contrast-enhanced MRI examination of any body region including central nervous system (CNS).

Secondary objectives:

1. To evaluate the safety of gadopiclenol (clinical and biological) up to 3 months following single administration.
2. To evaluate the efficacy of gadopiclenol-enhanced MRI by body region (CNS, vessels and pool of others) as assessed by on-site Investigator.

Trial design and methodology

This Phase II open-label, uncontrolled, multicenter trial is designed to investigate the pharmacokinetic (PK) profile of gadopiclenol in plasma, in pediatric patients aged up to 23 months inclusive (term neonates or preterm infants after the neonatal period), using a population PK approach. This approach, which allows sparse blood sampling, is selected to minimize the clinical burden to children. Blood sampling will be recommended via indwelling catheters rather than by repeated venipunctures.

A total of 3 blood samples per patient will be taken post-injection for PK analysis, one within each window:

- 10-60 minutes,
- 2-4 hours,
- 6-8 hours.

Each time window contains 4 time points for blood collection. One of the time points within each time window will be randomly allocated to the patients by Interactive Web Response System (IWRS).

Three age groups are defined:

- Group 1: patients aged 3 to 23 months (inclusive)
- Group 2: patients aged 28 days to less than 3 months
- Group 3: patients aged from birth to 27 days (term newborns).

The inclusions started with the oldest patients in Group 1.

The decision to start the inclusions in Group 2 was taken by the Trial Safety Review Board (TSRB) based on safety assessment over one-day period after injection of the first 13 patients in Group 1.

According to the protocol amendment N°2, the aged-down staggered approach is discontinued to allow the inclusions in Group 3 (patients aged from birth to 27 days), simultaneously to inclusions in

Group 1 and Group 2. The decision to start the inclusions in Group 3 will be implemented (if required country per country) upon the approval by CA and IRBs of the present amendment.

The inclusions in the three age groups will be completed in parallel.

However, the TSRB will continue to meet and review safety data, as described in the TSRB Plan.

Number of patients

50 patients will be included in the trial assuming that at least 45 patients will be evaluable for the primary criteria.

Patients will be distributed between the 3 age groups as following:

- Group 1: at least 20 patients
- Group 2: at least 12 patients
- Group 3: at least 5 patients

At least 25 patients (50%) will be scheduled to undergo contrast-enhanced MRI of CNS (CNS cohort)

Inclusion criteria:

1. Female or male pediatric patient aged from birth to 23 months of age inclusive (term neonates for all age groups or preterm infants after the neonatal period for groups 1 or 2). The neonatal period for preterm newborns is defined as the day of birth through the expected date of delivery plus 27 days. Term is defined as ≥37 completed weeks of amenorrhea,
2. Patient with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS,
3. Patient whose parent(s) or legal guardian (where applicable) having read the information has/have provided his/her/their consent to patient's participation in writing by dating and signing the informed consent form prior to any trial related procedure being conducted,
4. Patient affiliated to national health insurance according to local regulatory requirements.

Non-inclusion criteria:

1. Patient planned for treatment or procedure (e.g. surgery) that would prevent from obtaining the required blood samples or performing other trial procedures between the screening visit and up to one day after gadopiclenol administration,
2. Patient undergoing treatment or procedure (e.g., diuretics, clinically significant blood loss or blood transfusion) preceding or subsequent to gadopiclenol administration that would alter gadopiclenol pharmacokinetic parameters,
3. Patient with acute or chronic renal insufficiency defined as estimated Glomerular Filtration Rate (eGFR) out of age-adjusted normal value calculated based on bedside Schwartz equation,
4. Patient presenting with known class III/IV congestive heart failure according to the Modified Ross Heart Failure Classification in Children,
5. Patient with history of bleeding disorder,
6. Patient with known severe liver disease,
7. Patient with known cardiac arrhythmia (e.g., heart rhythm anomalies, long QT syndrome),

8. Patient with electrolyte or fluid imbalance that at Investigator's judgment presents undue risk assessed within one month prior to gadopiclenol administration,
9. Patient undergoing a change in chemotherapy (product or dosage) within one day prior to or one day after gadopiclenol administration,
10. Patient who received or will receive any other contrast agent for CT and/or MRI within one week prior to or one week after gadopiclenol administration,
11. Patient with contraindication for MRI such as iron metal implants (e.g., aneurysm clips, pacemaker),
12. Patient with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents,
13. Patient with history of hypersensitivity caused by any contrast media / agents (iodinated or gadolinium-based),
14. Patient with known contraindication(s) to the use of any gadolinium-based contrast agent (GBCA),
15. Patient with anticipated, current or past condition (medical with particular attention to prematurity, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate to the whole trial,
16. Patient unlikely to comply with the protocol, e.g., uncooperative attitude of parent(s) or legal guardian (where applicable), inability to return for follow-up visits and unlikelihood of completing the trial,
17. Patient having participated in a clinical trial and having received any investigational product within one week prior to or planned within one week after gadopiclenol administration,
18. Patient previously included in this trial,
19. Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

Investigational Medicinal Product (IMP) administration

Investigational Medicinal Product Name: gadopiclenol (formulation G03277.100)

Pharmaceutical form: 3 mL of sterile, clear, transparent ready-to-use aqueous solution for injection contained in vials of 10 mL.

Concentration: 0.5 M

Route and method of administration:

The IMP will be administered intravenously (IV) manually or by power injector (if the desired volume can be delivered by the injector) as a bolus injection at a recommended rate of 1-2 mL/sec. Contrast-enhanced MRI can start shortly after the injection depending on the pulse sequences used and the protocol for the examination. Gadopiclenol injection will be followed by a saline flush to ensure complete administration of the contrast.

Patients will be dosed according to their BW on the day of MRI examination. Gadopiclenol will be administered at a dose of 0.05 mmol/kg BW (0.1 mL/kg BW).

The patient participation starts from the signing of the Informed Consent Form at V1 (screening) and ends at V5 (3-month safety follow-up) or earlier in case of premature discontinuation.

The date of the last visit (date of the last procedure related to the visit) of the last patient undergoing the trial will correspond to the end of the trial.

Evaluation criteria

Primary criteria:

Gadopiclenol pharmacokinetics in plasma for pediatric patients aged up to 23 months (inclusive) will be assessed based on the 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.

Secondary criteria:

- The following clinical and biological safety parameters/examinations will be measured/performed:
  - Physical examination at visits 1, 2 (if applicable), 3, 4 and 5 including examination of general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities).
  - Vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO_2)) at 3 time points: prior to IMP injection, 10-60 min and 1 day after IMP injection.
  - Safety laboratory variables centrally analyzed (biochemistry and hematology) from blood samples collected prior to and 1 day after IMP injection,
  - Estimated glomerular filtration rate (eGFR) centrally calculated based on the bedside Schwartz equation prior to and 1 day after IMP injection,
  - Tolerance at the injection site at 3 time points: during injection, 10-60 min and 1 day after IMP injection,
  - Adverse events (AE) occurring from the beginning of patient's participation in the trial (Informed Consent Form signature) until the end of the participation.
  - Clinical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit. In case of suspicion of NSF a deep skin biopsy will be performed.
- Efficacy will be assessed by the on-site radiologist for both pre-contrast (Pre) and pre+post contrast (Paired) images, assessments will be performed for the primary anatomical area to be evaluated based on following parameters:
  - Technical adequacy for diagnosis using a 4-point scale: non diagnostic (reasons to be provided), poor, fair and good.
  - Assessment of overall contrast quality using a 5-point scale: 1= None (for example, in case of a non-enhancing lesion), 2= Poor, 3= Moderate, 4= Good, 5= Excellent.
  - Number and location of lesions/abnormal vessels, the largest diameter (lesions only) of three most representative lesions/abnormal vessels will be recorded.
  - Quantitative assessment (not applicable for vessels): percentage of enhancement (E%) and Lesion to Background Ratio (LBR) and Contrast to Noise Ratio (CNR) for CNS only for up to 3 most representative lesions (largest enhancing lesions).
  - Lesion/vessel visualization (border delineation, internal morphology and degree of contrast enhancement) for up to 3 most representative lesions or vessel abnormalities using a 4-point scale for each parameter.

- Change in diagnosis from Pre to Paired MRI.
- Change in diagnostic confidence from Pre to Paired MRI. Diagnostic confidence is assessed using a 5-point scale: 1 = nil: very uncertain, 2 = poor: uncertain, 3 = moderate: moderately certain, 4 = high: good certainty, 5 = excellent: very certain
- Change in treatment plan from Pre to Paired MRI.

Statistical methods

The sampling design was evaluated by simulation for 45 and 40 infants using gadopiclenol pop PK model validated in pediatric patients from 2 to 17 years of age refined to account for renal maturation in infants. With 45 infants, the sampling design is considered as appropriate to collect informative samples for the determination of PK in the infant population. An important between-subject variability on volumes of distribution is anticipated, which does not invalidate the sampling design being of limited interest as far as the inter-individual variability (IIV) for clearance (CL) is correctly estimated.

Assuming that about 10% of patients included in the trial will not be evaluable for the primary criteria, a sample size of 50 patients, in agreement with the pediatric plans (PIP/PSP), will allow to achieve the study objectives.

There will be four patient sets defined for this trial:

- The All enrolled Patients Set will include all patients having the inform consent form signed by their parent(s)/legal guardian. This set will be used for patient disposition summaries and individual listings.
- The Full Analysis Set (FAS) will include all patients undergoing an enhanced MRI examination. This set will be used for Efficacy Analysis.
- The Safety Set will include all patients, receiving at least one administration of IMP. This set will be used for evaluation of safety and description of demographic data and baseline characteristics.
- The Per Protocol Set (PPS) will include all patients in the Safety Set without major deviations likely to impact the population PK model. This set will be used for population PK analysis and description of demographic data and baseline characteristics.

A population PK approach will be used to characterize gadopiclenol pharmacokinetics in children and hence determine pharmacokinetic parameters (concentrations at 10, 20 and 30 minutes post injection, Area Under the Curve, elimination half-life, total clearance, volume of distribution). Descriptive statistical analysis for pharmacokinetic profile in plasma, clinical and biological safety and gadopiclenol-enhanced MR efficacy evaluation will be performed.

TRIAL FLOW CHART

Visit Number	V1	V2					V3	V4	V5
Time points	Screening visit	Inclusion Visit confinement period					1-day safety follow-up	1-week safety follow-up	3-month safety follow- up
	≤ 7 days before inclusion	Day 1					Day 2	Day 8	Day 90
Evaluation/procedures		Prior to IMP injection	T0 IMP injection	W1 10 - 60 min	W2 2 – 4 h	W3 6 - 8 h	V2 + 1 day	V2 + 7 days ± 1 days	V2 + 89 days ± 7 days
Informed consent signature	X								
Eligibility criteria	X	X							
Patient number assignment	X								
Demographic data	X	X							
Medical/surgical history/current medical condition	X								
Physical examination[1]	X	X[2]					X	X	X[3]
Vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO_2))		X		X			X		
Height	X								
Body weight		X							
Concomitant treatments[4]	◄								►
Blood sampling for biochemistry and hematology	X[5]						X		
IMP allocation via IWRS		X							
IMP administration			X						
Injection site tolerance			X	X			X		
MRI[6]			X						
Non-serious AE[7]	◄								►
SAE and AESI[8]	◄								►
Blood sampling for PK analyses[9]				X	X	X			

[1] Physical examination should be performed by a physician: examination of general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities). Information

indicating the global assessment (normal or abnormal (specify)) of the physical examination should be recorded on source documentation.

(2) Physical examination at V2 should be repeated if the time elapsed between V1 and V2 is > 3 days.

(3) Physical examination will include active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit. In case of suspicion of NSF a deep skin biopsy will be performed.

(4) Any medication, including homeopathic products, over-the-counter medications, as well as prescription drugs, on-going at V1 or administered until V4 will be recorded in the patient's eCRF. Between V4 and V5 safety visits, newly started concomitant medications/treatments in patients experienced at least one AE will be documented. Any GBCA injection will be documented in all patients.

(5) At screening, blood sample will be collected to analyse biochemistry and hematology in central lab including measurement of serum creatinine and eGFR calculation. If centrally calculated eGFR is not available at V2, serum creatinine and eGFR can be obtained locally to confirm patient's eligibility, fingerstick capillary blood sampling at the point of care is acceptable.

Note: In any case the overall trial-related blood loss (including potential capillary blood sampling at the point of care for locally calculated eGFR) 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).

(6) Contrast-enhanced MRI duration will correspond to the usual practice at site depending on the indication.

(7) All Adverse Events occurring from the beginning of the patient's participation in the trial (Informed Consent Form signature) and until V4, must be reported and followed even if no IMP was administered.

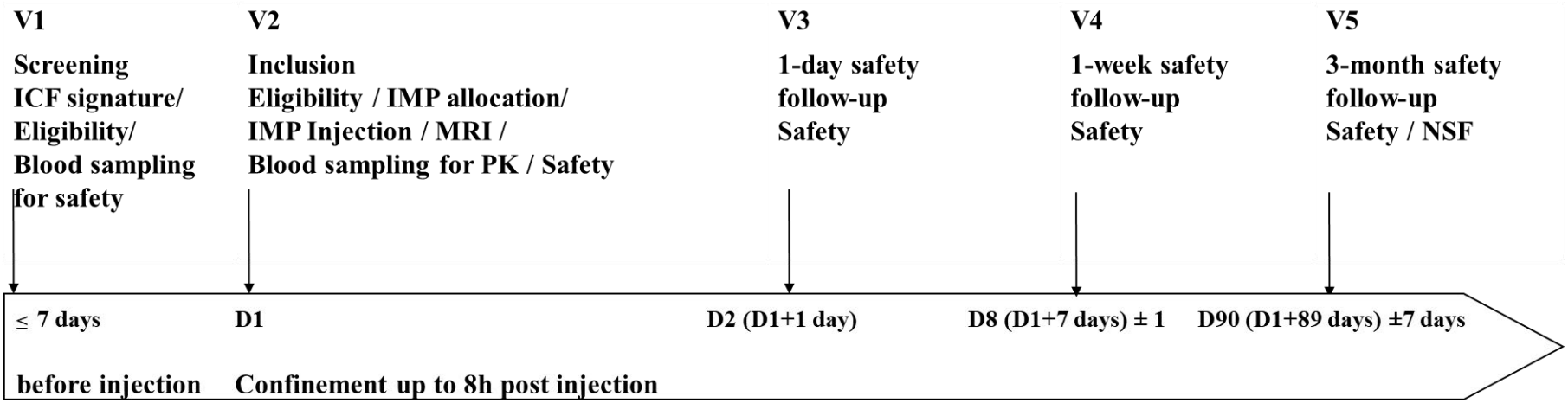
Non-serious AE occurring before IMP administration and not related to the trial can be collected as medical history or AE according to Investigator's opinion. Non-serious AEs occurring after V4 must be reported if related to the drug or to the trial and followed until recovery or sequelae stabilization.

(8) Serious Adverse Events (SAE) and Adverse Event of Special Interest (AESI) occurring from the beginning of the patient's participation in the trial (ICF signature) and until V5 must be reported and followed until recovery or sequelae stabilization (see 9.1.2).

(9) Three blood samples will be drawn per patient, one during each time window: W1, W2 and W3 at time points allocated by randomization via IWRS.

TRIAL DIAGRAM

Figure 1: Trial diagram



SIGNATURE PAGE

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

COORDINATING INVESTIGATOR PPD	Date: DD Mon YYYY

INVESTIGATOR STATEMENT

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

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

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
CA	Competent Authority
CL	Clearance
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form/ electronic Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
Cr	Creatinine
DMC	Data Monitoring Committee
EBEs	Empirical Bayes Estimates
EMA	European Medicine Agency
ENT	Ears, nose, throat
ESRD	End Stage Renal Disease
EU-QPPV	European Qualified Person for Pharmacovigilance
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IIV	Inter-Individual Variability
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
IWRS	Interactive Web Response System
MRI	Magnetic Resonance Imaging
PD	Pharmaco Dynamics

PIL	Patient Information Leaflet
PK	Pharmacokinetic
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SS	Safety Set
SXS	Screened Patient/Healthy Volunteer/Subject Set (i.e. SPS, SHVS, SSS)
SUSAR	Suspected Unexpected Serious Adverse Reaction

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

AMENDMENT 3 (Applicable to all countries)

List of Protocol Amendments

DOCUMENT HISTORY	
Document	**Date**
Protocol V1.0	03-Sep-2021
Protocol V2.0 Amendment 1	21-Jul-2022
Protocol V3.0 Amendment 2	24-Jun-2023
Protocol V4.0 Amendment 3	09-Oct-2023

Overall Rationale for the Amendment:

Per previous protocol versions, blood samples for PK were to be collected from a peripheral intravenous line, using a catheter placed in the forearm (contralateral to the IMP injection site).

However, considering the study population it seems difficult to place and maintain a peripheral intravenous line in young children for the duration of PK sampling. To avoid any burden due to blood sampling during the confinement period, this amendment 3 allows the collection of PK samples from the same line used for the IMP injection, considering that the saline flush after IMP injection will eliminate all remnants of IMP from the line, or alternatively the use of a capillary specimen (for example heel-pricks or finger pricks), in the event of any difficulties to place and/or maintain the peripheral intravenous line into a vein. The rationale for using capillary specimen is that it is the most pain-free blood-sampling procedure in paediatrics and neonatology [1] and allows to collect the small quantities of blood required for PK analyses. There is no reason to consider any difference in IMP dosing in capillary blood versus venous blood.

Modified and new text is shown in **bold font** and deleted text in ~~strikethrough~~.
Few other changes implemented in the amendment are linked to minor typo corrections.
This amendment makes changes to the following sections of the protocol. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis, trial flow chart and trial diagrams.

Version Date		**21-JULY-2022**	**XX-XXX-2023**
Page	**Section**	**WAS**	**IS**
45	5.1	… Injection and blood sampling ~~must~~ be performed through different IV lines. …	… **IMP** injection and **blood** sampling should **preferably** be performed through different IV lines. **For more details regarding blood sampling for PK, please refer to Section 8.5.2.** …

55	8.1.2.2	… The start of gadopiclenol administration is set as time point 0 (T0). ~~Intravenous catheters will be inserted (a patient IV line will be established) for the blood samples collection in the forearm (contralateral to the injection site) or in the feet.~~ ~~…~~ After IMP administration the patient will stay at the trial site at least until last blood sampling for PK analysis scheduled ~~within W3~~ (6-8 hours after gadopiclenol injection).	… The start of gadopiclenol administration is set as time point 0 (T0). … After IMP administration the patient will stay at the trial site at least until last blood sampling for PK analysis scheduled (6-8 hours after gadopiclenol injection). **More details regarding blood sampling for PK are provided in 8.5.2.**
58	8.5.2	A peripheral catheter will be placed for blood collection during the confinement period (in the forearm contralateral to the injection site) ~~or in the feet~~. During the ambulatory period, blood samples will be collected by direct venipuncture. 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. Injection and sampling will be performed through different IV lines. … Blood samples of 600 µL each will be collected at each time point for analysis.	A peripheral catheter will be placed for blood collection during the confinement period **preferably** ~~(~~in the forearm contralateral to the **IMP** injection site). During the ambulatory period, blood samples will be collected by direct venipuncture. 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. **Preferably, IMP** injection and blood sampling **for PK** will be performed through different IV lines. **Alternatively, the same IV line can be used for both IMP injection and blood sampling for PK. A washout with saline, after IMP injection and before collecting blood sample, must eliminate all remnants of IMP from the needle/line. In the event there is no possibility to perform venous sampling, blood samples for PK will be collected through a capillary specimen (for example heel-pricks or finger pricks at investigator's discretion).** … Blood samples of 600 µL each will be collected at each time point for analysis **(regardless of the blood sampling site)**
83	16	…	**1. WHO guidelines on drawing blood: best practices in phlebotomy - best practices in phlebotomy** …

AMENDMENT 2 (Applicable to all countries)

List of Protocol Amendments

DOCUMENT HISTORY	
Document	**Date**
Protocol V1.0	03-Sep-2021
Protocol V2.0 Amendment 1	21-Jul-2022
Protocol V3.0 Amendment 2	24-Jun-2023

Overall Rationale for the Amendment:

The patient recruitment and inclusion were initially based on an aged-down staggered approach, starting with the oldest patients aged 3 to 23 months inclusive (Group 1). The decision to start the inclusions in Group 2 (patients aged 28 days to less than 3 months) was taken by the Trial Safety Review Board (TSRB) based on review and assessment of both clinical and safety data (AEs, Laboratory data including eGFR, vital signs and physical examinations) over one-day period after injection of the first 13 patients in Group 1. There were no safety concerns raised.

Considering the conclusions of the above-mentioned TSRB as well as the safety profile of Gadopiclenol similar to other Gadolinium Based Contrast Agents (GBCA) already evaluated in pediatric patients less than 2 years old [19; 20], and based on the recommendation from FDA, it is considered safe to discontinue the aged-down staggered approach and allow the inclusions in Group 3 (patients aged from birth to 27 days), simultaneously to inclusions in Group 1 and Group 2. The decision to start the inclusions in Group 3 will be implemented (if required country per country) upon the approval by CAs and IRBs of the present amendment. To further support this amendment, the clinical and safety data over one-day period after injection of the first 25 patients in Group 1 will be reviewed during an upcoming ad-hoc TSRB, to ensure no safety data have been raised.

The main changes in this amendment are implemented to discontinue the aged-down staggered approach and consequently to allow inclusion of patients simultaneously in the three following age groups:

- Group 1: patients aged 3 to 23 months (inclusive)
- Group 2: patients aged 28 days to less than 3 months
- Group 3: patients aged from birth to 27 days (term newborns).

Furthermore, other changes implemented are as follows:

- The inclusion criteria 2 is updated to clarify that it is not mandatory for patients to have previous imaging examinations,
- Exceptional circumstances related to COVID-19 restrictions are removed, due to the end of COVID-19 pandemic.

Modified and new text is shown in **bold font** and deleted text in ~~strikethrough~~.
Few other changes implemented in the amendment are linked to minor typo corrections.
This amendment makes changes to the following sections of the protocol. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis, trial flow chart and trial diagrams.

Version Date		21-JULY-2022	24-JUNE-2023
Page	**Section**	**WAS**	**IS**
36	1.2	(…) At the time of this protocol amendment ~~1~~ submission, the following clinical data in adults and pediatrics are already available: (…) The indication for dose adaptation based on age was excluded. Comparable plasma gadopiclenol concentrations for different age groups of children within the time window relevant for MRI were predicted to be achieved with body weight-based dosing. Positive efficacy results and good safety profile of gadopiclenol was demonstrated when used in the pediatric population aged 2 to 17 years. Two phase III trials have been conducted in 256 adult patients with CNS indications (GDX-44-010) and 304 adult patients with other body regions indications (GDX-44-011). Both trials showed the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg compared to unenhanced MRI and the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement). Good safety profile of gadopiclenol at 0.05 mmol/kg was confirmed by both trials. (…)	(…) **Safety of GBCA in pediatric population less than 2 years old, has already been evaluated in the previous studies, with no new specific risk identified in those studies as well as post marketing data from GBCA (19-20).** At the time of this protocol amendment 2 submission, the following clinical data in adults and pediatrics are already available: (…) The indication for dose adaptation based on age was excluded. Comparable plasma gadopiclenol concentrations for different age groups of children within the time window relevant for MRI were predicted to be achieved with body weight-based dosing. Positive efficacy results and good safety profile of gadopiclenol was demonstrated when used in the pediatric population aged 2 to 17 years **[27]**. Two phase III trials have been conducted in 256 adult patients with CNS indications (GDX-44-010) and 304 adult patients with other body regions indications (GDX-44-011). Both trials showed the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg compared to unenhanced MRI and the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement). Good safety profile of gadopiclenol at 0.05 mmol/kg was confirmed by both trials **[28-29]**. (…)
38	1.3	Based on the available results of the above-described trials performed with gadopiclenol, the Benefit/Risk ratio is considered positive, and no serious safety concern is anticipated for the pediatric patients, who will be enrolled in the present trial~~, including Japanese pediatric patients~~. The risk related to the physiology of term newborns includes volume of contrast agent distribution which may be different from those in older children because of different body water and fat content. In addition, renal clearance mechanisms are immature and rapidly changing. (…)	Based on the available results of the above-described trials performed with gadopiclenol, the Benefit/Risk ratio is considered positive, and no serious safety concern is anticipated for the pediatric patients, who will be enrolled in the present trial. The risk related to the physiology of term newborns includes volume of contrast agent distribution which may be different from those in older children because of different body water and fat content. In addition, renal clearance mechanisms are immature and rapidly changing. (…)

39	3.1	(…) At least 25 patients (50%) will be scheduled to undergo a contrast-enhanced MRI of CNS (CNS cohort). ~~Inclusion will be performed using an age-down staggered approach. The inclusions will start with the oldest patients (Group 1) and end with the youngest patients (Group 3).~~ ~~The decision to start the inclusion of infants in Group 2 will be taken by the Trial Safety Review Board (TSRB) based on safety assessment over one day period after injection of the first 10 patients in Group 1.~~ ~~The decision to start the inclusion in Group 3 will be taken by TSRB based on safety assessment over one day period after injection of the first 6 patients included in Group 2 (Figure 3).~~ ~~The previous age group will be completed in parallel with the start of the next group.~~ (…)	(…) At least 25 patients (50%) will be scheduled to undergo a contrast-enhanced MRI of CNS (CNS cohort). (…)
42	3.3.1	(…) Maximum trial duration for each patient: 104 days ~~(Under exceptional circumstances, in case of Covid 19 related restrictions and if V5 is postponed, maximum trial duration may increase up to 127 days)~~.	(…) Maximum trial duration for each patient: 104 days.
42	3.5	Trial Safety Review Board (TSRB) described in 12 is ~~established to~~: • ~~assess the safety data at intervals and to decide whether to continue, modify, or stop the trial;~~ • ~~decide to start the enrollment of the next age down group based on the safety assessment in the previously included patients.~~	Trial Safety Review Board (TSRB), described in 12, is **responsible for**: • **ensuring the participants' safety;** • **appraising the trial conduct and progress;** • **making a decision on providing green light for next age group (when applicable);** • **making a decision concerning the continuation, modification, or termination of the trial.** **Full details regarding the TSRB will be provided in the TSRB plan.**
43	4.1	(…) 2. Patient with known or highly suspected abnormalities/ lesion(s) ~~as detected by previous imaging examinations (including the fetal imaging~~), scheduled to undergo contrast-enhanced MRI of any body region including CNS, (…)	(…) 2. Patient with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS, (…)

46	5.3.1	(…) IWRS will ensure that at least 25 patients (50%) are scheduled for contrast-enhanced MRI of CNS. ~~F~~irst enrollment in the ~~next~~ age group 2 w~~ill be~~ conditioned by the decision of the TSRB. The inclusion will continue until the overall number reaches 50 patients. (…)	(…) IWRS will ensure that at least 25 patients (50%) are scheduled for contrast-enhanced MRI of CNS. **The f**irst enrollment in the age group 2 w**as** conditioned by the decision of the **first** TSRB. **Based on the good safety profile of gadopiclenol, following amendment 2, the inclusions in the age group 3 will be opened simultaneously to inclusions in age groups 1 and 2.** The inclusions will continue until the overall number reaches 50 patients. (…)
56	8.1.4	(…) ~~Under exceptional circumstances, in case of Covid 19 related restrictions, sponsor may authorize investigator to inquire remotely about AE and concomitant medications and/or postpone visit up to 1 month maximum.~~	(…)
57	8.1.5	(…) ~~Under exceptional circumstances, in case of Covid 19 related restrictions, sponsor may authorize investigator to inquire remotely about AE and concomitant medications and/or postpone visit up to 1 month maximum.~~	(…)
68	10.4	(…) ~~Screen failure or premature discontinuation of patient is related to Covid 19, Yes/ No;~~	(…)
76	12	(…) TSRB is responsible for the careful review of the safety data of first 10 patients in Group 1 in order to take a decision to start the inclusion in Group 2. ~~then of the first 6 patients included in Group 2 take a decision to start the inclusion in Group 3~~. (…)	(…) **A TSRB plan, developed for this trial, describes the TSRB composition and defines roles and responsibilities of the TSRB members. The TSRB meetings will take place as defined in the TSRB plan.** TSRB is responsible for the careful review of the safety data of first 10 patients in Group 1 in order to take a decision to start the inclusion in Group 2. **Then, the TSRB will continue to meet as defined in the TSRB plan (via scheduled and ad-hoc meetings whenever deemed necessary).** (…)

83	16	(…) 27. Jurkiewicz E., Tsvetkova S, Grinberg A, Pasquiers B. Pharmacokinetics, Safety, and Efficacy of Gadopiclenol in Pediatric Patients Aged 2 to 17 Years. Invest Radiol. 2022; 57: 510-516. 28. Loevner LA, Kolumban B, Hutoczki G, et al. Efficacy and Safety of Gadopiclenol for Contrast-Enhanced MRI of the Central Nervous System: The PICTURE Randomized Clinical Trial. Invest Radiol. 2023;58(5):307-13. 29. Kuhl C, Csőszi T, Piskorski W, et al. Efficacy and safety of half-dose gadopiclenol versus fulldose gadobutrol for contrast-enhanced body MRI. Radiology. 2023 (in press). 30. Ross, R.D. The Ross Classification for Heart Failure in Children After 25 Years: A Review and an Age-Stratified Revision. Pediatr Cardiol 33, 2012; 1295–1300.	(…) **27. Jurkiewicz E., Tsvetkova S, Grinberg A, Pasquiers B. Pharmacokinetics, Safety, and Efficacy of Gadopiclenol in Pediatric Patients Aged 2 to 17 Years. Invest Radiol. 2022; 57: 510-516.** **28. Loevner LA, Kolumban B, Hutoczki G, et al. Efficacy and Safety of Gadopiclenol for Contrast-Enhanced MRI of the Central Nervous System: The PICTURE Randomized Clinical Trial. Invest Radiol. 2023;58(5):307-13.** **29. Kuhl C, Csőszi T, Piskorski W, et al. Efficacy and safety of half-dose gadopiclenol versus fulldose gadobutrol for contrast-enhanced body MRI. Radiology. 2023 (in press).** **30.** Ross, R.D. The Ross Classification for Heart Failure in Children After 25 Years: A Review and an Age-Stratified Revision. Pediatr Cardiol 33, 2012; 1295–1300.

1 INTRODUCTION

1.1 Trial Rationale

Magnetic Resonance Imaging (MRI) is an important modality used in children for detection, evaluation, staging, and follow-up of lesions mostly in the central nervous system (CNS) diseases. MRI is applied for a range of CNS disease processes such as tumors (e.g. ependymoma, medulloblastoma, cerebellar low-grade astrocytoma), congenital malformations, demyelinating diseases, neurodegenerative diseases, inflammatory diseases, epilepsy and infections. In addition to CNS imaging, MRI is also very helpful in anatomic imaging of chest, abdomen, pelvis, cardiovascular and musculoskeletal systems for disorders including congenital malformations, tumors, infections, metabolic disorders, and inflammatory diseases. Comparing to other imaging modalities (such as ultrasound, X-ray, computed tomography [CT]) available in children, MRI offers the major safety advantage of a lack of ionizing radiation, combined with efficacy benefits of excellent three-dimensional anatomic representation, tissue characterization, and quantitative/functional capabilities [2].

Gadolinium-based contrast agents (GBCA) provide reliable enhancement on T1-weighted images and represent the clinical standard in many pediatric MRI protocols. MRI with GBCAs improves the localization, characterization, and staging of tumors/lesions, the differentiation of inflammatory and infective disorders.

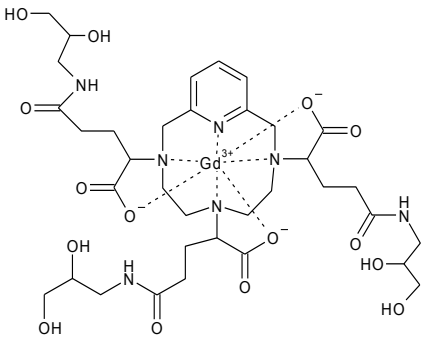
For GBCAs, r1-relaxivity is the primary determining factor for contrast efficacy. Most of the GBCAs available have similar T1 relaxation time, except for gadobenate dimeglumine (MultiHance®), its r1-relaxivity is approximately 1.5 to 2-fold higher than other agents with standard relaxivity. A series of intra-individual comparative studies have demonstrated measurable differences in image preference and diagnostic performance for gadobenate dimeglumine [3-7].

However, gadobenate dimeglumine belongs to linear GBCAs, and some of the recently published studies showed gadolinium retention in the brain related to linear agents [8-13] even though clinical consequence of this finding is still under investigation. Gadolinium retention raises special concern in the potentially vulnerable pediatric patient population. Therefore, there is a medical need to have a macrocyclic agent with a high relaxivity for diagnosing and monitoring a wide range of childhood diseases.

In contrast to linear chelates, the macrocyclic chelates offer a strong binding to Gd^{3+} by the virtue of being preorganized rigid rings of almost optimal size to cage the gadolinium atom [14].

Gadopiclenol is a new paramagnetic, macrocyclic, non-ionic GBCA developed for intravenous (IV) use during MRI. Its molecular weight is 970.11 g/mol and chemical structure is presented in Figure 2.

Figure 2: Chemical structure of gadopiclenol



Gadopiclenol is used as an aqueous injectable solution for injection at a concentration of 0.5M.

Gadopiclenol has demonstrated at least two-fold higher T_1 relaxation time compared to other available GBCAs including gadobenate dimeglumine and therefore is expected to have better contrast efficacy, i.e. clinically relevant increases in signal enhancement or meaningful increase in lesion number or lesion extent compared with other "standard relaxivity" GBCAs.

The macrocyclic structure of gadopiclenol makes it a more stable complex than the linear ones. This is supported by stability studies. As a macrocyclic GBCA, gadopiclenol is expected to have a very low risk for brain retention of gadolinium [15]. Therefore, a good long-term safety is anticipated.

Several published studies have documented the pharmacokinetic (PK) profiles of GBCAs in children. All patients have received a single intravenous injection of 0.1 mmol/kg of GBCA; serum and urine (whenever applicable) samples were analyzed for total gadolinium to describe their pharmacokinetic profile. The results show similar pharmacokinetic values obtained in pediatric population to those observed in adults [16-21]. The previous PK trial with gadopiclenol in children aged from 2 to 17 years demonstrated no indication for dose adaptation based on age in addition to body weight-based dosing.

The present trial will analyze the PK profiles of gadopiclenol in children younger than 2 years of age after a single injection of the same dosage of 0.05 mmol/kg BW, a half as high as dosage of other GBCAs used in children. Based on efficacy demonstrated in older children and adults in 2 phase III studies this dosage is expected to provide satisfactory efficacy.

The current trial population will be limited to pediatric patients with normal renal function scheduled to undergo a contrast-enhanced MRI of CNS and any other body region. This trial is part of the Pediatric Investigation Plan (PIP) and Pediatric Study Plan (PSP) agreed with EMA and FDA respectively.

1.2 Background

Extensive non-clinical study program performed on gadopiclenol showed a very satisfactory safety profile supporting the clinical development in adults and pediatric patients.

Safety of GBCA in pediatric population less than 2 years old, has already been evaluated in the previous studies, with no new specific risk identified in those studies as well as post marketing data from GBCA [**20-21**].

At the time of this protocol amendment 2 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 [25].

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 subjects: 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-finding 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. Dose 0.05 mmol/kg was identified as the lowest dose showing efficacy similar to the reference product [26].

A phase I trial in patients with renal insufficiency (GDX-44-005) included 5 successive cohorts of 8 subjects: healthy volunteers (cohort 1) and patients with mild (cohort 2), moderate (cohort 3), severe (cohort 4) and end stage renal disease (ESRD) (cohort 5). Urinary and blood long term elimination were evaluated up to 6 months following gadopiclenol injection at a dose of 0.1 mmol/kg. The trial showed a good safety profile of gadopiclenol. After a single intravenous injection, the gadopiclenol is eliminated predominantly by renal clearance: the elimination half-life is increasing with the degree of renal impairment (mean $t_{1/2}$ of 1.9 h, 3.3 h, 3.8 h and 11.7 h in cohort 1, 2, 3 and 4, 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 trial did not raise any concern [27].

A phase II popPK trial (GDX-44-007) has been conducted in 80 pediatric patients aged 2 to 17 years with CNS and Body pathologies. Long term safety was evaluated up to 3 months after the injection. The popPK model developed in this trial was robust and the pharmacokinetics of gadopiclenol were best described using a two-compartment model with elimination from the central compartment. Minor difference was observed between pediatric age groups and adults due to the non-linear relationship between body weight and clearance. The indication for dose adaptation based on age was excluded. Comparable plasma gadopiclenol concentrations for different age groups of children within the time window relevant for MRI were predicted to be achieved with body weight-based dosing. Positive efficacy results and good safety profile of gadopiclenol was demonstrated when used in the pediatric population aged 2 to 17 years [**28**].

Two phase III trials have been conducted in 256 adult patients with CNS indications (GDX-44-010) and 304 adult patients with other body regions indications (GDX-44-011). Both trials showed the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg compared to unenhanced MRI and the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement). Good safety profile of gadopiclenol at 0.05 mmol/kg was confirmed by both trials [**29-30**].

A phase I PK single center, ascending dose, double blind, randomized, placebo control trial (GDX-44-013) has been conducted in 27 Japanese healthy volunteers with dosages 0.025, 0.05 and 0.1 mmol/kg aiming to establish pharmacokinetic (plasma and urine) profile of gadopiclenol following single administration at ascending dose levels. Good safety profile was confirmed in Japanese healthy volunteers following gadopiclenol administration.

1.3 Benefit/Risk Assessment

Based on the available results of the above-described trials performed with gadopiclenol, the Benefit/Risk ratio is considered positive, and no serious safety concern is anticipated for the pediatric patients, who will be enrolled in the present trial. The risk related to the physiology of term newborns includes volume of contrast agent distribution which may be different from those in older children because of different body water and fat content. In addition, renal clearance mechanisms are immature and rapidly changing. However previous studies with other GBCAs in this vulnerable population demonstrated similar PK profile between adults and children and adequacy of body weight-based dosing for term newborns [21].

2 TRIAL OBJECTIVES

2.1 Primary Objective

To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection of 0.05 mmol/kg body weight (BW) in pediatric population aged up to 23 months (inclusive) scheduled for a contrast-enhanced MRI examination of any body region including central nervous system (CNS).

2.2 Secondary Objectives

1. To evaluate the safety of gadopiclenol (clinical and biological) up to 3 months following single administration.
2. To evaluate the efficacy of gadopiclenol-enhanced MRI by body region (CNS, vessels and pool of others) as assessed by on-site Investigator.

3 TRIAL DESCRIPTION

3.1 Protocol Design

This Phase II open-label, uncontrolled, multicenter, international trial is designed to investigate the pharmacokinetic (PK) profile of gadopiclenol in plasma, in pediatric patients aged up to 23 months inclusive (term neonates or preterm infants after the neonatal period), using a population PK approach. This approach, which allows sparse blood sampling, is selected to minimize the clinical burden to children. The 2-compartment model with elimination from the central compartment validated in adults and older children was used to optimize the trial design and PK sampling time. Blood sampling will be recommended via indwelling catheters rather than by repeated venipunctures.

A total of 3 blood samples per patient will be taken post-injection for PK analysis, one within each window:

- 10-60 minutes,
- 2-4 hours,
- 6-8 hours.

Each time window contains 4 time points for blood collection (Table **1: Sampling time points randomly allocated.**). One of the time points within each time window will be randomly allocated to the patients by IWRS (Interactive Web Response System).

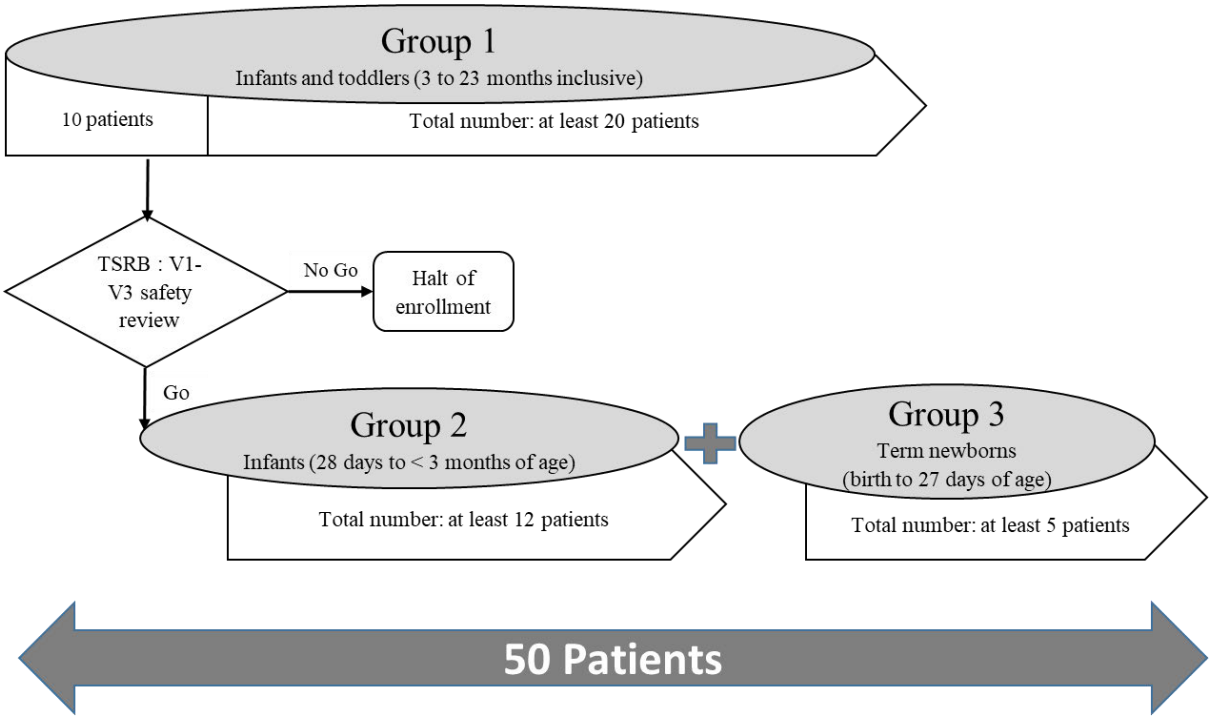
The total sample size of 50 patients will be distributed between 3 age groups as following:

- Group 1: at least 20 patients aged 3 to 23 months (inclusive)
- Group 2: at least 12 patients aged 28 days to less than 3 months
- Group 3: at least 5 patients aged from birth to 27 days (term newborns)

At least 25 patients (50%) will be scheduled to undergo a contrast-enhanced MRI of CNS (CNS cohort).

Any patient who has received an IMP injection without major deviations, will be considered evaluable for the primary criteria.

Figure 3: Enrollment Diagram



3.2 Justification for dose

One Investigational Medicinal Product (IMP) dose of 0.05 mmol/kg will be injected in all patients. This "key clinical dose" was assessed for safety and efficacy in adults and older pediatric patients in previous studies and will be proposed for regulatory approval in USA and Europe.

3.3 Trial Duration

3.3.1 *Duration of patients participation*

Each patient will undergo 5 visits:

- V1 - Screening: up to 7 days before inclusion;
- V2 - Inclusion: between D1 (gadopiclenol administration) and the end of confinement period;
- V3 – 1-day safety follow-up;
- V4 – 1-week safety follow-up;
- V5 – 3-month safety follow-up to monitor NSF risk.

Patient eligibility is appraised at screening visit and takes place up to 7 days before inclusion. The minimum duration between screening and inclusion visits will be restricted by the availability of laboratory results to confirm that all inclusion/non-inclusion criteria are met.

MRI is performed prior to and after gadopiclenol administration on MR systems (1.5T or 3T). The start of administration is considered as IMP injection time point (T0). The end of confinement period will be determined by the last sampling time point randomly allocated within window 6-8 hours.

Overall expected trial duration for each patient is about 3 months:

- Minimum trial duration for each patient: 83 days
- Maximum trial duration for each patient: 104 days.

Patient participation starts from the signing of the Informed Consent Form at V1 (screening) and ends at V5 (3-month safety follow-up) or earlier in case of premature discontinuation.

3.3.2 *End of trial*

A patient is considered to have completed the trial if he/she has completed all phases of the trial including the last visit shown in the Trial Flow Chart.

The end of the trial is defined as the date of the last scheduled procedure shown in the trial Flow Chart for the last visit of the last patient.

3.4 Interim Analysis

None.

3.5 Trial Committee(s)

Trial Safety Review Board (TSRB), described in 12, is responsible for:

- ensuring the participants safety,
- appraising trial conduct and progress
- making a decision on providing green light for next age group (when applicable)
- making a decision concerning the continuation, modification, or termination of the trial
- .
-

Full details regarding the TSRB will be provided in the TSRB plan.

4 PATIENT SELECTION

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

4.1 Inclusion Criteria

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

1. Female or male pediatric patient aged from birth to 23 months of age inclusive (term neonates for all age groups or preterm infants after the neonatal period for groups 1 or 2). The neonatal period for preterm newborns is defined as the day of birth through the expected date of delivery plus 27 days. Term is defined as ≥37 completed weeks of amenorrhea,

2. Patient with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS,
3. 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,
4. Patient affiliated to national health insurance according to local regulatory requirements.

4.2 Non-Inclusion Criteria

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

Non-inclusion criteria:

1. Patient planned for treatment or procedure (e.g. surgery) that would prevent from obtaining the required blood samples or performing other trial procedures between the screening visit and up to one day after gadopiclenol administration,
2. Patient undergoing treatment or procedure (e.g., diuretics, clinically significant blood loss or blood transfusion) preceding or subsequent to gadopiclenol administration that would alter gadopiclenol pharmacokinetic parameters,
3. Patient with acute or chronic renal insufficiency defined as estimated Glomerular Filtration Rate (eGFR) out of age-adjusted normal value calculated based on bedside Schwartz equation,
4. Patient presenting with known class III/IV congestive heart failure according to the Modified Ross Heart Failure Classification in Children [31],
5. Patient with history of bleeding disorder,
6. Patient with known severe liver disease,
7. Patient with known cardiac arrhythmia (e.g., heart rhythm anomalies, long QT syndrome),
8. Patient with electrolyte or fluid imbalance that, at Investigator's judgment, presents undue risk assessed within one month prior to gadopiclenol administration,
9. Patient undergoing a change in chemotherapy (product or dosage) within one day prior to or one day after gadopiclenol administration,
10. Patient who received or will receive any other contrast agent for CT and/or MRI within one week prior to or one week after gadopiclenol administration,
11. Patient with contraindication for MRI such as iron metal implants (e.g., aneurysm clips, pacemaker),
12. Patient with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents,
13. Patient with history of hypersensitivity caused by any contrast media / agents (iodinated or gadolinium-based),
14. Patient with known contraindication(s) to the use of any gadolinium-based contrast agent (GBCA),

15. Patient with anticipated, current or past condition (medical with particular attention to prematurity, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate to the whole trial,
16. Patient unlikely to comply with the protocol, e.g., uncooperative attitude of parent(s) or legal guardian (where applicable), inability to return for follow-up visits and unlikelihood of completing the trial,
17. Patient having participated in a clinical trial and having received any investigational product within one week prior to or planned within one week after gadopiclenol administration,
18. Patient previously included in this trial,
19. Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

4.3 Patient Identification

When the parents or legal guardian (where applicable) signed the written informed consent form, the patient will be allocated a unique Identification Number (patient ID).

Any patient for whom an informed consent has been signed will be considered as a 'screened' patient.

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

5 INVESTIGATIONAL MEDICINAL PRODUCTS

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

- European Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals

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

The IMP will consist of a vial individually 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 Description

Gadopiclenol (formulation G03277.100), 3 mL of sterile, clear, transparent ready-to-use aqueous solution for injection, is contained in vials of 10 mL, concentrated at 0.5 M.

Gadopiclenol is administered intravenously (IV) manually or by power injector (if the desired volume can be delivered by the injector) as a bolus injection at a recommended rate of 1-2 mL/sec). Contrast-enhanced MRI can start shortly after the injection depending on the pulse sequences used and the protocol for the examination. Gadopiclenol injection will be followed by a saline flush to ensure complete administration of the contrast.

A patient IV line should be established and maintained throughout the examination. 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).

Wherever possible trial specific blood sampling will be performed when routine clinical samples are obtained. Patients who might be at risk for a particular reaction during the contrast agent injection (patients with history of bronchial asthma, allergy etc.) should receive added surveillance (e.g., carefully monitored pulse and blood pressure).

IMP injection and blood sampling should preferably be performed through different IV lines. For more details regarding blood sampling for PK, please refer to Section 8.5.2.

MRI examination of the patient will be immediately discontinued if a serious adverse event (SAE) occurs during or just after injection of the contrast agent (preventing post-contrast imaging sequences).

Patients will receive a single dose of gadopiclenol calculated according to their BW on the day of MRI examination. Gadopiclenol will be administered at a dose of 0.05 mmol/kg BW (0.1 mL/kg BW). A qualified professional according to local regulation) will be responsible for preparing the dosing solutions.

For more information on gadopiclenol please refer to the Investigator’s Brochure.

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 will be performed by Guerbet.

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

IMP will consist in one box that contains one 10-mL vial with 3mL of gadopiclenol.

In case of damaged IMP, 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 individual and under the conditions described in the Investigator's Brochure. The IMPs should be stored at a temperature of 25°C or below in the original package, protected from light and not frozen.

At the time of the trial completion, all used (including empty vials) and unused IMPs should have been returned to the Sponsor or to the predefined location for storage before destruction. Destruction at site can be considered as an option if it is expressly authorized by Guerbet and subject to the reconciliation validated by Guerbet.

5.3 Condition of Investigational Medicinal Product Allocation

5.3.1 *Investigational Product Allocation*

A central web randomization system or IWRS (Interactive Web Response System) will be used to manage inclusion of patients in the trial, allocation of sampling time points (one of 4 within each time window as per Table **1: Sampling time points randomly allocated.**) and IMP allocation. Once eligibility criteria are confirmed, Patient Identification Number will be recorded into the system.

IWRS will ensure a balanced distribution of the trial population between 3 predefined age groups as following:

- Group 1: at least 20 patients aged 3 to 23 months (inclusive)
- Group 2: at least 12 patients aged 28 days to less than 3 months
- Group 3: at least 5 patients aged from birth to 27 days (term newborns)

IWRS will ensure that at least 25 patients (50%) are scheduled for contrast-enhanced MRI of CNS.

The first enrollment in the age group 2 was conditioned by the decision of the first TSRB. Based on the good safety profile of gadopiclenol, following amendment 2, the inclusions in the age group 3 will be opened simultaneously to inclusions in age groups 1 and 2. The inclusions will continue until the overall number reaches 50 patients.

IMP number will be independent from the Patient Identification Number.

The dose of gadopiclenol to be administered will be rounded to one decimal and calculated based on patient's BW with one decimal fraction.

In case of problem of IMP allocation (e.g. wrong IMP administered to a patient), the site must immediately report the incident to Guerbet and the IWRS provider in order to ensure that all corrective actions are taken. Corrective actions may include transferring the IMP to quarantine to prevent further

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

5.3.2 *Double-Blind Conditions*

Not applicable. The IMP will be administered in an open-label fashion.

5.3.3 *Individual Trial Treatment Unblinding*

Not applicable.

5.4 Investigational Medicinal Product Management

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

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

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

5.5 Auxiliary Medicinal Product and Other Trial Products

Not applicable.

5.6 Trial Product Compliance and Accountability

A 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. It is recommended not to discard immediately the injection material (syringe, tubing) but to keep them at site for one week to investigate the IMP administration conditions if necessary. 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 electronic Case Report Form (eCRF).

6 CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

Any medication, including homeopathic products, pre-medication, over-the-counter medications, as well as prescription drugs, on-going at the time of patient's parent(s) or legal guardian (where applicable) informed consent signed or administered until V4 (1-week safety follow-up) will be recorded in the patient's eCRF.

Between V4 and V5 safety visits, newly started concomitant medications/treatments in patients experienced at least one AE will be documented. Any GBCA injection will be documented in all patients.

The following information must be provided:

- Drug (brand name or generic name)
- Route of administration
- Purpose (medical history/trial disease/AE/pre-medication/prophylaxis)
- Indication
- Start/end period.

6.1.1 *Concomitant Medications of Special Attention*

In order to limit any interference with the safety and efficacy evaluation of Investigational Product, the following precaution and restriction must be considered:

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 eCRF. Treatments used for general sedation or topical anesthesia or other non-pharmacological 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 GBCA, and therefore, no specific hydration procedure is defined in this protocol. Nonetheless, whenever possible, the patient's parents or legal guardian (where applicable) should be instructed to give a patient to drink water and other fluids liberally before and after the injection.

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

6.1.2 *Prohibited Concomitant Medications*

A minimum of 1-week wash-out is required between any other contrast agent administration for CT and/or MRI and gadopiclenol injection. At least 1 week must elapse between trial contrast-enhanced MRI and any subsequent contrast agent administration.

Any medication preceding or subsequent to the gadopiclenol administration that would alter gadopiclenol pharmacokinetic parameters (e.g., treatment with diuretics), is not permitted.

Any change in chemotherapy is prohibited within 1 day prior to and 1 day after gadopiclenol administration.

6.2 Concomitant Procedures

Any procedure performed during the trial and related to any reported AE will be recorded in the patient eCRF. At least the following information must be provided:

- Name of procedure
- Indication
- Duration

Any intervention that would prevent from obtaining the required blood samples or performing other trial procedures (e.g., surgery) is not permitted between the screening visit and up to 1 day after gadopiclenol administration.

Any procedure preceding or subsequent to the gadopiclenol administration that would alter gadopiclenol pharmacokinetic parameters (e.g., blood transfusion), is not permitted.

7 EVALUATION CRITERIA

7.1 Primary Criteria

Gadopiclenol pharmacokinetics in plasma for pediatric patients aged up to 23 months (inclusive) will be assessed based on the 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 bioanalytical protocol will describe the gadopiclenol assays in plasma samples. Those assays will be performed by Eurofins ADME BIOANALYSES, 75A avenue de Pascalet, 30310 Vergèze, France.

7.2 Secondary Criteria

7.2.1 *Clinical and biological safety*

- Physical examination at visits 1, 2 (if applicable), 3, 4 and 5 including examination of general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities).
  Any clinically significant abnormality or change will be recorded as AE or medical history if examination performed prior to IMP administration upon Investigator's judgement.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse rate and peripheral oxygen saturation (SpO_2)) at 3 time points: prior to IMP injection, 10-60 min and 1 day after IMP injection.

  Body temperature will be measured on forehead by infrared thermometer.

  Blood pressure and pulse rate will be measured after a rest for at least 5 minutes in supine position. Blood pressure will not be measured on the arm used for the injection.

  Peripheral oxygen saturation (SpO2) will be measured by pulse oximetry using a transcutaneous non-invasive light emitter.

  If significant change in vital signs occurs, vital signs should be measured more frequently as long as necessary to ensure that the change has been resolved and/or that the subject is stable. Any clinically significant abnormality or change will be recorded as AE or medical history if vital signs performed prior to IMP administration upon Investigator's judgement.
- Safety laboratory variables centrally analyzed (biochemistry and hematology) from blood samples collected at screening and 1 day after IMP injection.

- Hematology: red blood cells (RBCs), white blood cells (WBCs) counts: neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, mean red blood cells volume (MCV).
- Biochemistry: sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, total protein, calcium, phosphorus, iron, ferritin, transferrin, total bilirubin, conjugated bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), PT (prothrombin time) / INR (International Normalised Ratio).

- Estimated glomerular filtration rate (eGFR) calculated by central lab based on the bedside Schwartz equation prior to and 1 day after IMP injection.

  Bedside Schwartz equation [2222-24] will be used with creatinine methods with calibration traceable to isotope dilution mass spectroscopy (IDMS):
  eGFR (mL/min/1.73 m^2) = (0.413 × Height in cm) / Standardized Serum creatinine (mg/dl)

  Post-contrast acute kidney injury (PC-AKI) is defined as an increase in sCr of ≥ 0.3 mg/dl or sCr ≥1.5 times baseline. Such changes will be monitored, and additional information may be requested to the Investigator.

  Any clinically significant abnormal value or change will be recorded as AE. Any abnormal value on sampling performed prior to IMP administration could be recorded in medical history upon Investigator's judgement.
- Tolerance at the injection site (eruption, extravasation and inflammation) at 3 time points: during injection, 10-60 min and 1 day after IMP injection.
- Adverse events (AE) occurred from the beginning of patient's participation in the trial (Informed Consent Form signature) until the end of the participation.
- Clinical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit. In case of suspicion of NSF a deep skin biopsy will be performed.

7.2.2 *Gadopiclenol-enhanced MRI (Pre and Paired (pre+post)) efficacy evaluation*

Gadopiclenol-enhanced MRI efficacy will be assessed by on-site radiologist for both pre-contrast (Pre) and pre+post contrast (Paired) images, based on following parameters:

- Technical adequacy for diagnosis using a 4-point scale: poor, fair, good or non-diagnostic If non-diagnostic, reasons will be provided:
  - 1 = Artifacts due to patient
  - 2 = Artifacts due to machine
  - 3 = Injection technical failure
  - 4 = Inadequate anatomic coverage
  - 5 = Other, please specify
- Assessment of overall contrast quality using a 5-point scale: 1= None (for example, in case of a non-enhancing lesion), 2= Poor, 3= Moderate, 4= Good, 5= Excellent.
- Number and location of lesions/abnormal vessels and largest diameter (lesions only) of three most representative lesions/abnormal vessels will be recorded.

- Quantitative assessment (not applicable for vessels): percentage of enhancement (E%) and Lesion to Background Ratio (LBR) and Contrast to Noise Ratio (CNR) for CNS only for up to 3 most representative lesions (largest enhancing lesions).

- **Percentage of enhancement (E%) of lesion** will be calculated by using the equations below:

$$\mathbf{E\%} = \frac{\boldsymbol{SI_{post} - SI_{pre}}}{\boldsymbol{SI_{pre}}}\mathbf{x100}$$

where SI_{post} = SI of lesion on post injection T1 weighted images;
SI_{pre} = SI of lesion on pre injection T1 weighted images.

  - Measurements of the signal intensity (SI) of the lesion will be performed on the pre and post-injection identical T1 weighted sequences.

- **Lesion to Background Ratio on post-injection T1 weighted images (LBRpost) will** be calculated by using the equations below:

$$\boldsymbol{LBRpost} = \frac{\boldsymbol{SI_{post}}}{\boldsymbol{SI_b}}$$

where SI_{post} = SI of lesion on post injection T1 weighted images;
SI_b = SI of background (surrounding healthy tissue of the lesion) on post injection T1 weighted images.

- **Contrast to Noise Ratio on post-injection T1 weighted images (CNRpost) for CNS only**

$$\boldsymbol{CNRpost} = \frac{\boldsymbol{SI_{post} - SI_{ht}}}{\boldsymbol{SD_{noise}}}$$

where SI_{post} = SI of lesion on post injection T1 weighted images;

SI_{ht} = SI of surrounding healthy tissue in brain or spinal cord on post injection T1 weighted images;
SD_{noise} = Standard Deviation (SD) of background noise on post injection T1 weighted images.

  - Measurements of the SI of the lesion are to be made on the best representative images of the pathology. The ROI for a lesion will encompass a homogeneous area within the lesion as large as possible.
  - For healthy tissue measurements, ROI should be placed in normal appearing homogeneous brain or spinal cord.
  - Measurements of the background noise SD are to be placed on the slice where corresponding lesion is located. The ROI should be placed outside head or spine but within imaging FOV.

- Lesion/vessel visualization (border delineation, internal morphology and degree of contrast enhancement) using a 4-point scale for each parameter.

  The Investigator will record each of lesion/vessel visualization parameters (lesion border delineation, internal morphology and degree of contrast enhancement) for up to 3 most representative lesions or vessel abnormalities.

  - Border delineation:

Delineation of the lesion/vessel border is defined as the distinction of lesion or vessel from surrounding tissues. 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 or vessel includes an identification of lesion architecture and the internal features and homogeneity of vessel enhancement. This criterion will be assessed through the following scale:

- 1 = poor: poorly seen
- 2 = moderate: majority of lesion or vessel is poorly seen
- 3 = good: majority of lesion or vessel is clearly seen but with minor parts of lesion or vessel invisible
- 4 = excellent: lesion or vessel is well seen.

▪ Degree of contrast enhancement:

This criterion will be a qualitative assessment according to the following scale:

- 1 = no: lesion or vessel is not enhanced
- 2 = moderate: lesion or vessel is weakly enhanced
- 3 = good: lesion or vessel is clearly enhanced
- 4 = excellent: lesion or vessel is clearly and brightly enhanced

o Change in diagnosis from Pre to Paired MRI: yes/no/not assessable

o Change in diagnostic confidence from Pre to Paired MRI, defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a patient: yes/no/not assessable

The diagnostic confidence will be assessed through the following scale:

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

When the investigator chooses ‘not assessable’ for diagnosis, by definition the confidence level is 1 (= very uncertain).

o Change in treatment plan from Pre to Paired MRI: yes/no/not assessable

The Investigator will document therapeutic management proposed based on both pre-contrast (Pre) and pre+post contrast (Paired) MRI (surgery, biopsy, chemotherapy, radiotherapy, other treatment)

8 TRIAL SCHEDULE AND PROCEDURES

8.1 Trial Schedule

Day 1 is defined as the day of IMP injection.

8.1.1 *Screening Visit – Visit 1 – ≤ 7 days before inclusion*

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

- Written informed consent for the participation of the patient in the trial prior to any trial related procedure will be obtained from parent(s) or legal guardian (where applicable) as described in 13.3;
- The patient will be attributed an Identification Number in chronological order;
- Verification of all eligibility (inclusion/non-inclusion) criteria;
- Recording of demographic data: sex, race/ethnicity and date of birth;
- Recording of relevant medical/surgical history/current medical condition present before signing the informed consent including trial disease;
- Recording of indication for current contrast-enhanced MRI;
- Recording of patient's previous contrast agent exposure (type of contrast agent administered, number of examination with the product, related adverse reaction);
- Physical examination, including: general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities);
- Measurement of height;
- Medications and treatments on-going at the time of signing informed consent;
- Blood sample for analyses in Central Lab (hematology and biochemistry);
- Estimated glomerular filtration rate (eGFR) centrally calculated based on the bedside Schwartz equation must be used if available at the time of inclusion to check the non-inclusion criterion. Otherwise, serum creatinine and eGFR can be obtained locally to confirm patient's eligibility, fingerstick capillary blood sampling at the point of care is acceptable; Inclusion visit (Visit 2) to be scheduled.

8.1.2 *Inclusion Visit – Visit 2 – Day 1*

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

- Any change in on-going medication/treatment since V1;
- Recording and assessment of AEs occurred since V1 as described in 9.1.2;
- Safety follow up on the next day (Visit 3) to be scheduled.

8.1.2.1 Prior to gadopiclenol injection

- Verification of all eligibility (inclusion/non-inclusion) criteria;
- Check the age to ensure that the patient still belongs to the assigned age group;
- Physical examination if the time elapsed between V1 and V2 is > 3 days;

- Measurement of vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO_2) by pulse oximetry using a transcutaneous non-invasive light emitter);
- Measurement of body weight and calculation of volume to be injected;
- Recording of any change in on-going or new medication and treatment since last visit;
- Recording and assessment of AEs occurred since screening visit (V1) as described in 9.1.2;
- IWRS connection will be done to obtain the IMPs box number.

8.1.2.2 Time point T0

The start of gadopiclenol administration is set as time point 0 (T0).

- Injection site tolerance (eruption, extravasation, inflammation) will be evaluated and any event will be reported as adverse event;
- Volume of IMP actually injected will be recorded.

After IMP administration the patient will stay at the trial site at least until last blood sampling for PK analysis scheduled (6-8 hours after gadopiclenol injection). More details regarding blood sampling for PK are provided in 8.5.2.

MRI scans will be acquired before and after gadopiclenol injection.

8.1.2.3 Time window W1

The following tasks will be performed within first time window (10-60 min after gadopiclenol injection):

- Blood sample will be collected for PK analysis. Actual sampling time must be recorded;
- Injection site tolerance (eruption, extravasation, inflammation) will continue to be evaluated and any event will be reported as adverse event;
- Vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO_2) transcutaneous non-invasive pulse oximetry using a light emitter) will be measured. If significant changes in vital signs occur, vital signs should be recorded more frequently and for as long as necessary, to ensure that the changes are resolved, and/or that the patient is stable.

8.1.2.4 Time windows W2 and W3

The following task will be performed within second-and third-time windows (2-4h and 6-8h) after gadopiclenol injection respectively:

- Blood sample will be collected for PK analysis. Actual sampling time must be recorded.

8.1.3 *Safety Follow Up – Visit 3 – Day 2*

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

- Physical examination, including: general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities);
- Injection site tolerance (eruption, extravasation, inflammation) will continue to be evaluated and any event will be reported as adverse event;

- Vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO_2) by pulse oximetry using a transcutaneous non-invasive light emitter) will be measured. If significant changes in vital signs occur, vital signs should be recorded more frequently and for as long as necessary, to ensure that the changes are resolved, and/or that the patient is stable;
- Blood sample for analyses in Central Lab (hematology and biochemistry);
- eGFR centrally calculated based on the bedside Schwartz equation;
- Any change in on-going medication/treatment since V2 or new concomitant medications/treatments will be documented;
- Recording and assessment of AEs occurred since V2 as described in 9.1.2;
- Safety follow up (Visit 4) to be scheduled.

8.1.4 *Safety Follow Up – Visit 4 – Day 8±1 day*

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

- Physical examination, including: general appearance, skin (including extremities), neck (including thyroid), eyes, abdomen, back, lymph nodes, peripheral vascular and neurological examination and other (any other observed abnormalities);
- Any change in on-going medication/treatment since V3. New concomitant medications/treatments will be documented if the patient experienced at least one AE;
- Recording and assessment of AEs occurred since V3 as described in 9.1.2;
- Safety follow-up (Visit 5) to be scheduled.

8.1.5 *Safety Follow Up – Visit 5 – Day 90±7 days*

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

- Physical examination will consist in active detection of Nephrogenic Systemic Fibrosis (NSF)-related symptoms including: burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness. In case of suspicion of NSF a deep skin biopsy will have to be performed. In case of the detection of one or more of the listed symptoms that lead to suspect NSF, a report form for SAE or AESI must be completed and reported.
- New concomitant medications/treatments since V4 will be documented if the patient experienced at least one AE;
- Any GBCA injection since the last visit will be documented;
- Other concomitant medications/treatments will be documented if related to the reported AE;
- Recording and assessment of related AEs, all SAE and AESI occurred since V4 as described in 9.1.2.

8.2 Imaging Characteristics

8.2.1 *Equipment*

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

8.2.2 *Imaging protocol*

MRI scans will be acquired before and after gadopiclenol injection. The same parameter setting for the same sequence before and after injection should be used for each patient.
The imaging sequences/parameters will be performed according to site's standard imaging protocol. Yet, T1 weighted images before and after injection must be obtained.

8.3 On-Site Reading of Images

For each investigational site, at least one experienced radiologist will be appointed at the start of the trial, it is highly advised to have the same radiologist to read the images of all patients included at the site. Back up radiologist(s) might be involved.

GUERBET will document the imaging tasks and obligations of the investigational site and imaging evaluation in an Imaging Manual. GUERBET's representative will ensure that the imaging can be performed by the site and that the Imaging Manual will be accurately followed by the Investigator.

The Investigator will report required evaluation results in the eCRF.

8.4 Off-Site Reading of Images

Not applicable. However, it is request that investigational sites should submit anonymous images to GUERBET in a format agreed prior to trial start.

8.5 Non-Imaging Central procedures

Details on handling blood samples will be provided to the site in a trial specific manual.

8.5.1 *Central laboratory for biological assessments*

A central laboratory will be used for all scheduled laboratory tests in this trial except for eGFR which can be assessed both, locally to check the non-inclusion criterion 3 and centrally for safety evaluation. Bedside Schwartz equation will be used for calculation of the eGFR. This formula will be used by central laboratory with creatinine methods with calibration traceable to isotope dilution mass spectroscopy (IDMS):

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = (0.413 \times \text{Height in cm}) / \text{Standardized Serum creatinine (mg/dl)}$$

The central laboratory will provide the necessary kits to collect the blood samples and will also provide appropriate information regarding shipping of the samples.

Care should be taken during blood sampling to avoid potential generation of false positive blood value (e.g., by inappropriate use of the tourniquet or forceful withdrawal of blood). Each original laboratory report will be filed with the patient's source document.

All laboratory reports must be promptly reviewed by the Investigator, and upon review, initialed and dated by the Investigator. For all laboratory assessments, the laboratory will flag values falling outside of the normal ranges on the laboratory report. All abnormal values considered clinically significant according to Investigator's judgment will be reported as AEs or medical history if sample collected before IMP injection and documented in the patient's source document. Further measurements will be performed when the Investigator considers the need to follow any abnormal value until the parameter returns to initial value or stabilizes.

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

8.5.2 *Blood sampling for PK*

A peripheral catheter will be placed for blood collection during the confinement period preferably in the forearm contralateral to the IMP injection site.

During the ambulatory period, blood samples will be collected by direct venipuncture. 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. Preferably, IMP injection and blood sampling for PK will be performed through different IV lines. Alternatively, the same IV line can be used for both IMP injection and blood sampling for PK. A washout with saline, after IMP injection and before collecting blood sample, must eliminate all remnants of IMP from the needle/line. In the event there is no possibility to perform venous sampling, blood samples for PK will be collected through a capillary specimen (for example heel-pricks or finger pricks at investigator's discretion).

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 randomization, as per the Table 1**: Sampling time points randomly allocated.** below, at the inclusion visit. Exact time of sample collection will be recorded.

Table 1: Sampling time points randomly allocated.

Time Window	Sampling time within Time Window (allocated by randomization)
W1: 10 min to 60 min post-injection	**W1.1:** 10 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 600 µL each will be collected at each time point for analysis (regardless of the blood sampling site). In any case the overall trial-related blood loss (including potential capillary blood sampling at the point of care for locally calculated eGFR) 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).

For gadopiclenol analysis, blood will be collected into 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 analytical centre in separate shipments.

Details on laboratory samples handling will be provided to the investigational sites in a specific lab manual.

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), suspected drug-drug interaction with another product (symptomatic or not) will also be reported to Guerbet.

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

9.1 Adverse Event

9.1.1 *Definition of Adverse Event*

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

An AE can therefore be:

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

Any disease identified and diagnosed by trial imaging examination with contrast agent will not be considered as AE. It may be collected in eCRF 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 course of the trial has to be considered as an AE.

9.1.2 *Collection and recording of Adverse Events*

The Investigator or his/her designee will invite the patient's parent or legal guardian (where applicable) 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 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 Table 2**: Collection and reporting of AEs throughout and after the trial.** below.

Table 2: Collection and reporting of AEs throughout and after the trial.

Visits and types of AEs to be reported	**V1 - Screening Visit**	**V2 - Inclusion Visit**	**V3 - 1-day safety follow-up**	**V4 - 1-week safety follow-up**	**V5 - 3-month safety follow- up**
	≤ 7 days before inclusion	D1	D2	D8±1day	D90±7days
Not related non-serious AEs	X*	X	X	X	
Not related SAEs	X	X	X	X	X
AESIs	X	X	X	X	X
Related**AEs (serious or not)	X	X	X	X	X

* 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.

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

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 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.
- **Date of the event end** (or consolidation)**:** This date is the date when the event has come to its ends or to its initial intensity (for the events that had been an aggravation of a pre-existing disorder). If the AE is still ongoing by the time of end of trial follow-up for the patient (i.e. last trial visit), the patient should be followed-up until AE resolution or a justification should be provided by the Investigator (i.e. chronic disease) in the medical file.
- **Causal relationship to the IMP:**
  - Related: the definition of adverse reaction (AR) implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

- Not related: Applicable when no IMP has been administered (pre-administration period) or when no causal relationship exists between the trial drug and the event, but an obvious alternative cause exists (e.g. the patient's underlying medical condition or concomitant therapy).

- **Causal relationship to a trial procedure (blood test, imaging procedure itself etc…):**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the procedure. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no procedure was performed yet or when no causal relationship exists between the trial procedure and the event, but an obvious alternative cause exists (e.g. the patient's underlying medical condition or concomitant therapy).
- **Outcome:**
  - Recovered/resolved: the AE is no longer present at any intensity or return to baseline intensity (for pre-existing disorders) or values for biological data.
  - Recovered/resolved with sequelae: the AE is resolved but residual effects are still present (to be specified on the AE form).
  - Not recovered/not resolved: the AE is still present at the last contact with the patient.
  - Fatal: this AE caused or directly contributed to the patient's death.
- **Action taken with regard to administration of the IMP:**
  - No action: for AE occurring during the pre-treatment/procedure after the post-treatment/procedure period, or if the IMP dosing/administration would not change in spite of the occurrence of the AE
  - IMP interrupted: the IMP administration is interrupted during the administration (e. g. extravasation…).
  - IMP definitively discontinued: the event leads to a definite contra-indication to the drug (e.g. confirmed hypersensitivity…).
- **Other action taken:**
  - AE-targeted medication: the patient was given a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the eCRF ("concomitant medication" section).
  - Other AE-targeted action: therapeutic measures other than corrective drug administration (e.g. ice, heating pad, brace, cast…) or patient underwent a procedure (surgery, physiotherapy, additional laboratory test…) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the eCRF ("procedures/therapeutic measures" section).
  - Trial discontinuation: the AE leads to a trial discontinuation,
- **Adverse event of special interest (AESI)** should be indicated (see 9.3.3 for AESI definition)
- **Assessment of the seriousness of the AE**: see 9.2 for SAE definition.

9.2 Serious Adverse Event

9.2.1 *Definition of Serious Adverse Event*

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

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

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

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

- Life-threatening in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Hospitalization refers to an admission and overnight stay at the hospital due to the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

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

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

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

- Any hospitalization that had been planned before the trial and that will take place during the trial, provided there is no aggravation of the disease to which it is related.
- Hospitalizations, which are not associated to an adverse event (such as hospitalization for check-up).

No anticipated SAE is defined in this protocol as no specific pathology is anticipated for patient inclusion.

9.2.2 *Reporting Serious Adverse Events (SAE)*

All SAEs **must be reported immediately** by the Investigator to Guerbet. Therefore, the Investigator must immediately forward to Guerbet Pharmacovigilance department a duly completed report form for SAE or AESI (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**

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

+ 33 (0)1 45 91 50 00.

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

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

- Patient's details including date of birth/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 or AESI duly completed (F001406).

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

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

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

According to local requirements, Guerbet or its representatives will communicate relevant safety information to the appropriate Agency(ies), 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 or drug-device interaction with another product.
- Unusual Lack of efficacy: for Guerbet imaging products, lack of efficacy is mainly represented by cases of "lack of contrast " or " poor iconographic quality " or "no contrast" or "poor contrast" etc.
- Overdose: administration of dose above the 0.3 mmol/kg for gadopiclenol.

9.3.2 *Pregnancy*

Not applicable.

9.3.3 *Adverse Events of Special Interest*

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

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

The AESI for this protocol is the following: Nephrogenic Systemic Fibrosis (NSF).

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

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

9.4 Other important safety issue / new fact

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

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

- A SAE which could lead to the modification of the conduct of the trial (ex: SAE associated with the trial procedures, SUSAR).
- A significant hazard to the patient population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease (if applicable).
- 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/TSRB, if any, where relevant for the safety of patient,
- Increase in the frequency of an expected event considered as clinically significant.

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

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

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

9.5 Unblinding Procedures

Not applicable.

10 SCREEN FAILURE AND PREMATURE DISCONTINUATION

10.1 Screen failure

A patient whose parent(s) or legal guardian (where applicable) have signed the informed consent and who discontinue the trial before IMP injection will be considered screening failure. The reason for screening failure will be documented. Such patient can be re-screened according to the same modalities as for the new patient. Particular attention must be paid in order not to exceed overall trial-related blood loss 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.

A new patient number will be allocated to the patient.

Data to be collected for screen failure patients: refer to 14.3.2

10.2 Premature Discontinuation of the trial per Guerbet Decision

Guerbet reserves the right to discontinue the trial at any time for medical, administrative or other reasons.

Guerbet will inform the relevant authorities in each country, the ethics committees, the trial site Investigators, pharmacists and hospital authorities according to the regulatory texts in force.

10.3 Premature discontinuation of the patient

Premature discontinued patients are defined as patients whose parent(s) or legal guardian (where applicable) have signed the informed consent and are discontinued from the trial after being administered with IMP.

Data collected for premature discontinued patients: Please refer to 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 parent(s) or legal guardian (where applicable) consent:

  If the patient's parent(s) or legal guardian withdraws consent for disclosure of future information, Guerbet may retain and continue to use any data collected before such a withdrawal of consent.

  If a patient withdraws from the trial, his/her parent(s) or legal guardian 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:
- Deviation from plan as specified in the protocol or deviation affecting primary criteria (e.g. trial specific assessment not performed):
- Other reason in case patient's screen failure or premature discontinuation is not related to any of the listed reasons

10.5 Enrollment of additional patient:

All patients prematurely discontinuing the trial for whom 3 blood sampling for PK analyses within 3time windows were not performed, will be replaced.

The enrollment will continue in order to ensure an overall number of 50 included patients (including 25 patients in CNS cohort) and minimum numbers of evaluable patients per age group (Group 1: at least 20 patients; Group 2: at least 12 patients and Group 3: at least 5 patients).

In the event of premature discontinuation, patients will receive adequate follow-up and usual medical care from 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

The trial aims to evaluate the pharmacokinetic plasma profile of gadopiclenol in a pediatric population aged from birth to 23 months. In order to minimize the clinical burden to children, only 3 samples per patients will be allowed, so, a population PK analysis, which is a suitable approach to characterize the PK with sparse blood sampling, will be performed to determine primary pharmacokinetic parameters. These parameters will be then summarized through descriptive statistics.

Therefore, no inference will be done from this trial and therefore no null or alternative hypotheses are needed.

11.2 Sample Size

The sample size was determined in order to optimize the characterization of gadopiclenol pharmacokinetics in pediatric population through population PK modelling. Sample size determination was coupled with evaluation of the PK sampling scheme recommended by FDA for the evaluation of the PK of Dotarem® in the same population of infants aged between 0 and 2 years [21].

Simulations were performed in order to evaluate the performance of the design and the sample size, using gadopiclenol popPK model for adult and children aged between 2 and 17 years refined to account for renal maturation in infants.

The design evaluation was performed for a sample size of 45 subjects evaluable for the primary criteria, as achieved in Dotarem® trial, and for 40 subjects.

Results were expressed as median of estimated parameters and precision (%RSE) calculated on successful estimation process performed on 200 simulated cases and presented in Table 3**: Evaluation of the design for 45 subjects.** and Table **4: Evaluation of the design for 40 subjects.** below.

Table 3: Evaluation of the design for 45 subjects.

Parameters	Typical values	Successful runs (/200)	Parameters Estimate	Bias	Precision (RSE%)
	Children	N	Median	Mean	Median
CL (L/H)	5.8	177	5.83	0.03	4.00
V1 (L)	7.76	177	7.47	-0.39	16.00
Q (L/H)	4.48	177	4.84	0.46	22.00
V2 (L)	4.41	177	4.63	0.18	14.00
IIV CL	0.0379	177	0.04	-0.00	27.00
IIV V1	0.0354	177	0.04	0.02	95.00

Parameters	Typical values	Successful runs (/200)	Parameters Estimate	Bias	Precision (RSE%)
	Children	N	Median	Mean	Median
IIV Q	NA	177			-
IIV V2	NA	177			-
σ	0.0372	177	0.04	-0.00	16.00

Table 4: Evaluation of the design for 40 subjects.

Parameters	Typical values	Successful runs (/200)	Parameters Estimate	Bias	Precision (RSE%)
	Children	N	Median	Mean	Median
CL (L/H)	5.8	168	5.85	0.03	4.00
V1 (L)	7.76	168	7.55	-0.27	16.00
Q (L/H)	4.48	168	4.73	0.44	23.00
V2 (L)	4.41	168	4.57	0.13	15.00
IIV CL	0.0379	168	0.03	-0.00	27.00
IIV V1	0.0354	168	0.04	0.03	97.00
IIV Q	NA	168	0.00	-	-
IIV V2	NA	168	0.00	-	-
σ	0.0372	168	0.04	-0.00	17.00

Overall, the sampling design with either 45 or 40 subjects will allow to estimate all fixed parameters with an excellent precision (RSE<=20%). The between subject variability for CL and residual error will be also very well captured (RSE<30%). Only the variability for the central volume of distribution could be poorly estimated if the infant's data cannot be combined with other data (stand-alone infant model). With only 3 samples to be taken by infant, it is anticipated that between-subject variability on volumes of distribution could not appropriately estimated, even with larger sample size, and this is not considered as a relevant issue invalidating the sampling design, because this variability is of limited interest as far as the IIV for CL is correctly estimated. Increasing the sample size will improve moderately the estimation of the between subject variability on volume of distribution, in case of infants' data cannot be pooled with other data collected in adult, children and adolescents.

Assuming that about 10% of patients included in the trial will not be evaluable for the primary criteria, a sample size of 50 patients, in agreement with the pediatric plans (PIP/PSP), will allow to achieve the trial's objectives.

11.3 Planned Analysis

11.3.1 *Disposition of patients*

Number of patients having signed the inform consent form, receiving the study drug and by visit will be presented per cohort (CNS, vessels and other body regions), age group and overall.

Number of screen-failed patients and reasons for screening failure before study drug administration will be provided per cohort, age group and overall.

Number of injected patients prematurely discontinued from the trial and reasons for trial discontinuation will be provided according to the cohort, age group and overall.

11.3.2 *Data Sets Analyzed*

There will be four patient sets defined for this trial:

- The All enrolled patients set will include all patients having the inform consent form signed by their parent(s)/legal guardian (where applicable). This set will be used for patient disposition summaries and individual listings.
- The Full Analysis Set (FAS) will include all patients undergoing an enhanced MRI examination. This set will be used for the Efficacy Analysis.
- Safety Set will include all patients, receiving at least one administration of IMP. This set will be used for evaluation of safety, description of demographic data and baseline characteristics.
- The Per Protocol Set (PPS) will include all patients in the Safety Set without major deviations likely to impact the population PK model. This set will be used for population PK analysis and description of demographic data and baseline characteristics.

11.3.3 *Protocol Deviations*

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

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

Any deviation(s) from the original statistical plan will be described and justified in the final report. Protocol deviations will be split in major and non major deviations. A major deviation is defined as a deviation having an impact on the primary criteria. At minimum following protocol deviations will be stated as major in the trial:

- Patient not administered with gadopiclenol
- No plasma PK sample was obtained
- Concomitant treatment or procedure (e.g., diuretics, clinically significant blood loss or blood transfusion) that may alter gadopiclenol pharmacokinetic parameters
- All information regarding time of injection and times of PK sampling is missing

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

Patients with major deviations will be excluded from the PPS.

PK modeling will be done using all patients of the PPS and sensitivity analyses could be conducted without data/patient identified as outliers.

Frequency and percentages of patients with non-major protocol deviations will be presented using the All enrolled Patients Set.

11.3.4 *Demographics and Baseline Characteristics*

All demographic and other baseline characteristics parameters will be summarised by cohort, age group and overall in the Safety Set and in PPS if different.

- Demographic parameters: age, sex, body weight, height, BMI, race/ethnicity.
- Other baseline characteristics: trial disease diagnosis, MRI examination, physical examination at screening, medical history, contrast media intolerance history and the prior medications / procedures defined as medications / procedures which stopped before IMP administration.

The main diagnosis will be coded using the MedDRA dictionary and tabulated by body system and preferred term

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 prior medications will be coded using the Anatomical Therapeutic Chemical (ATC) Drug dictionary and tabulated by ATC code.

Patient's prior procedures will be coded using the MedDRA dictionary and tabulated by body system, and preferred term.

11.3.5 *Compliance*

Volume theoretically administered (mL), volume actually administered (mL), theoretical volume actually administered (yes/no), absolute and relative difference between theoretical and actual volume will be displayed.

11.3.6 *Population PK analysis*

The population PK analysis will be performed on the PPS 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 Analyses*

All efficacy analyses will be done using the FAS and summarized per cohort and overall:

- Technical adequacy for diagnosis: results will be tabulated qualitatively for Pre and Paired (pre+post contrast) images. Shift tables between Pre and Paired scores will be provided.
- Assessment of overall contrast quality score will be tabulated qualitatively for Pre and Paired images. A shift tables between Pre and Paired scores will be provided.
- Evaluation of lesions/abnormal vessels: number and locations of detected lesions/abnormal vessels, and largest diameter (lesions only) of the 3 most representative lesions/abnormal vessels will be tabulated qualitatively and quantitatively respectively for Pre and Paired images.
- Assessment of contrast quality: signal intensity of lesion, percentage of enhancement (E%), LBR and CNR will be tabulated quantitatively.
- Lesion /vessel visualization (border delineation, internal morphology and contrast enhancement): for each parameter, score will be tabulated qualitatively for Pre and Paired images. A shift tables between Pre and Paired scores will be provided.
- Diagnosis (only for Pre MRI), diagnostic confidence, treatment plan for Pre and Paired MRI, change in diagnosis, change in diagnostic confidence and change in treatment plan from Pre to Paired MRI will be tabulated qualitatively.

11.3.8 *Adverse Event*

An overall summary of AEs will be presented using the All enrolled set to catch AEs of patients who did not receive trial drug. The table will be presented overall and only with the following variables:

- Total number of AEs

- Total number of patients with at least one AE

- Distribution of the number of AEs reported by patients (0, 1, 2 or 3 or more AEs)

- Total number of Serious AEs (SAEs)

- Total number of patients with at least one SAE

- Total number of AEs according to intensity (severity)

- Total number of patients with at least one AE according to intensity (severity)

- Total number of AEs according to the outcome

- Total number of patients with at least one AE according to the outcome

- Total number of AEs requiring a concomitant drug (other action taken)/procedure-Total number of patients with at least one AE requiring a concomitant drug (other action taken)/procedure

- Total number of AEs leading to the patient's withdrawal from the study Events will be classified as treatment-emergent (TEAE) if they started after drug administration.

The same overall summary will be displayed by age group for Treatment Emergent AEs (TEAEs) using the Safety Set. The following variables will be also presented:

- 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 trial IMP.

- Total number of TEAEs requiring withdrawal of trial IMP.

- Total number of patients with at least one TEAE requiring withdrawal of trial IMP.

The number and percentage of patients with at least one TEAE will be presented using the Safety Set by age group according to Primary SOC and PT.

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 age group according to Primary SOC and PT.

The number and percentage of patients with at least one SAE or AESI will be presented using the Safety Set by age group according to Primary SOC and PT.

The number and percentage of patients with at least one SAE or AESI with causal relationship to the IMP will be presented using the Safety Set by age group according to Primary SOC and PT.

11.3.9 *Laboratory data*

Safety laboratory data are defined as laboratory variables centrally analyzed (hematology and biochemistry) from blood samples, estimated glomerular filtration rate (eGFR) centrally calculated based on the bedside Schwartz equation (see 7.2.1). Safety laboratory data analysis will be done using the Safety Set.

The baseline is defined as the last measure before the IMP administration.

The statistical analysis will present results in Standard International (SI) units and conventional (CV) United States units. Original units will be only listed. Laboratory data will be analyzed quantitatively and qualitatively for each age group and overall. Qualitative analyses will be done via comparison of laboratory data to their reference ranges and according to their clinical significance. Quantitative analyses will be done by tabulating raw data and change from baseline.

The incidence of out-of-range results as well as shifts from baseline will also be presented by age group and overall.

11.3.10 *Other safety observations*

Other safety observations analysis will be done using the Safety Set.

11.3.10.1 Vital signs (temperature, blood pressure, pulse rate and peripheral (SpO_2) oxygen saturation (SpO2))

The baseline is defined as the last measure before the IMP administration.

Vital signs will be analyzed quantitatively and qualitatively for each age group and overall. Qualitative analyses will be done via comparison of vital signs data to their normal ranges and according to their clinically significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

11.3.10.2 Injection site tolerance

Number of patients experiencing eruption, extravasation and inflammation at site injection will be tabulated by time point, per age group and overall.

11.3.10.3 Physical Examination

Any new abnormality since the previous visit will be tabulated by time point, per age group and overall.

11.3.10.4 NSF Monitoring (clinical examination)

Number of patients with or without Nephrogenic Systemic Fibrosis (NSF) symptoms at 3 months will be provided for each age group and overall. In case of NSF, clinical evidence and results of the biopsy will be displayed for each age group and overall.

11.3.10.5 Extent of exposure

Duration between the ICF signature and the gadopiclenol injection, duration between IMP administrations and end of trial, site of administration, mode of injection (manual / power injector)., Actual rate of administration (mL/s) and volume of saline flush (mL) will be tabulated by age group and overall.

11.3.10.6 Concomitant medications / procedures

Frequency and percentages will be calculated for concomitant medications / procedures.

Concomitant medications / procedures are defined as medications / procedures which continue or start after IMP administration.

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

Patient's concomitant procedures will be coded using the MedDRA dictionary and tabulated by body system, and preferred term.

11.4 Specific statistical analytical considerations (not applicable for trial including only descriptive analysis)

Not applicable.

12 TRIAL COMMITTEES

Independent Data Monitoring Committee (IDMC).

An Independent Data Monitoring Committee (IDMC) will not be set up for this trial because the investigational site and Guerbet will be responsible to ensure the trial discontinuation rules are applied.

Trial Safety Review Board (TSRB)

Trial Safety Review Board (TSRB) is set up to perform a risk/benefit assessment during the recruitment period and for monitoring the overall conduct of the clinical trial as well as ensuring that criteria for early stopping are met.

A TSRB plan, developed for this trial, describes the TSRB composition and defines roles and responsibilities of the TSRB members. The TSRB meetings will take place as defined in the TSRB plan.

TSRB is responsible for the careful review of the safety data of first 10 patients in Group 1 in order to take a decision to start the inclusion in Group 2. Then, the TSRB will continue to meet as defined in the TSRB plan (via scheduled and ad-hoc meetings whenever deemed necessary).

Review of safety data at least until V3 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).

TSRB will not monitor the primary pharmacokinetic parameters.

The TSRB is composed as following: the international coordinator (or other identified medical expert in pediatric radiology) and GUERBET 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)
- 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
- European Parliament. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use; 2008.
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1) Current Step 4 version dated 5 February 1998
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Investigation of Medicinal Products in the Pediatric Population E11 Current Step 4 version dated 20 July 2000 and E11 (R1) Addendum dated 20 July 2017.
- Regulation (EU) 2016/679 Of The European Parliament And Of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 11 on Electronic Records; Electronic Signatures
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals
- Regional / local regulations and other specific populations regulations

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. Among all documents required locally, the approval and authorization must be obtained for the protocol, Investigator's Brochure, the patient parent(s) or legal guardian informed consent form and any other written information or document to be provided to the patients' parent(s) or legal guardian.

In case of modifications to the trial protocol, patients' parent(s) or legal guardian informed consent form or any other written information provided to the patients' parent(s) or legal guardian, 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 patient's safety may be at risk, Guerbet may implement emergency safety measures prior to obtaining IRB/IEC approval and Regulatory/Competent Authority opinion. In parallel to implementing these measures, Guerbet will immediately notify the concerned IRB/IEC and Regulatory/Competent Authorities of such implementation.

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

Notification of Serious Adverse Events/Reactions to IRB/IEC and Regulatory/Competent Authority will be made according to the national requirements. Safety reporting is described in section 9 of the present protocol.

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

13.3 Patient's parent(s) or legal guardian (where applicable) informed consent

Prior to participation, all patient's parent(s) or legal guardian (where applicable) must confirm their free and voluntary willingness to involve their child 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 of patients, rights and responsibilities of patient's parent(s) or legal guardian (where applicable), 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.

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

Patient's parent(s) or legal guardian may consent to participation of their child 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.

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

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

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

13.4 Trial Records and Archiving

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

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

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

At the end of the trial, investigational sites must ensure the ISF will be archived in an appropriate way that allows timely access and proper retention of documents. Retention period will be of at least 25 years after trial completion. Sites should obtain Guerbet written approval before destroying trial documents.

14 QUALITY CONTROL / QUALITY ASSURANCE

14.1 Direct Access to Source Data/Documents

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

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

The Investigator undertakes, in accordance with the regulation in force, to make anonymous any patient data before collection by Guerbet. Especially the name and address of the patients will be deleted from any medium such as eCRF, document for biological results, X-Ray films or digital supports. For this trial, the following will be considered as source data (as a minimum): patients' medical files, MR images.

- If computerized medical files are used, the system must be evaluated by Guerbet (or representative): in case printing of files is not possible, the computerized system must be validated and a secured access should be granted to Guerbet or its representative.

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

14.2 Clinical Monitoring

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

The representative will perform regular investigational site monitoring and report all discussions, patient and IMP data verification performed with particular attention to patient's 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.

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

The Investigator must attest:

- The authenticity of the data collected in the eCRF;

- The consistence between the data in the eCRF and those in the source documents, with the exception of those data recorded directly in the eCRF and considered as source data.

Results of evaluation of MR images can be recorded directly on the eCRF (i.e., no prior written or electronic record of data), and can be considered as 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 failed patients 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 serious adverse event (SAE). Additional information such as medical history, concomitant medication etc…might be requested in case of SAE.

For patients discontinued after the IMP administration, 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, PK data, imaging data, reason for premature discontinuation…). The Investigator must make every effort to collect and record all follow-up safety information (i.e., adverse events, injection-site tolerance, as appropriate), unless the patient's parent(s) or legal guardian withdraw consent for further data collection/participation for/in the trial.

14.3.3 *Data Management System*

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

Data processing and control will be closely managed by Guerbet's representative.

14.4 Audits and Inspections

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

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

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

The Investigator must allow the representatives of Guerbet (audit) and/or of the Competent/Regulatory Authorities (inspection):

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

15 PUBLICATIONS RULES

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

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

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

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

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

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

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

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

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

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

16 REFERENCES

1. WHO guidelines on drawing blood: best practices in phlebotomy - best practices in phlebotomy
2. Bhargava et al. Contrast-Enhanced Magnetic Resonance Imaging in Pediatric Patients: Review and Recommendations for Current Practice. Magnetic Resonance Insights.2013;6:95–111. doi:10.4137/MRI.S12561.
3. Maravilla KR, Maldjian JA, Schmalfuss IM, et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. Radiology. 2006; 240:389–400.
4. Kuhn MJ, Picozzi P, Maldjian JA, et al. Evaluation of intraaxial enhancing brain tumors on magnetic resonance imaging: intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for visualization and assessment, and implications for surgical intervention. J Neurosurg.2007;106:557–66.
5. Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MRimaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. AJNR Am J Neuroradiol.2008;29:1684–91.
6. Rumboldt Z, Rowley HA, Steinberg F et al. Multicenter, doubleblind, randomized, intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 Tesla. J Magn Reson Imaging.2009;29:760–67.
7. Seidl Z, Vymazal J, Mechl M et al. Does higher gadolinium concentration play a role in the morphologic assessment of brain tumors? Results of a multicenter intraindividual crossover comparison of gadobutrol versus gadobenate dimeglumine (the MERIT Study). AJNR Am J Neuroradiol.2012;33:1050–58.
8. Kanda T, Ishii K, Kawaguchi H et al. High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material. Radiology.2014;270:834–41.
9. Errante Y et al. Progressive Increase of T1 Signal Intensity of the Dentate Nucleus on Unenhanced Magnetic Resonance Images Is Associated With Cumulative Doses of Intravenously Administered Gadodiamide in Patients With Normal Renal Function, Suggesting Dechelation. Investigative Radiology.2014;49:685–90.
10. Quattrocchi C et al. High T1 Signal Intensity in Dentate Nucleus after Multiple Injections of Linear Gadolinium Chelates. Radiology.2015;276:616-17.
11. Weberling Lukas D. et al. Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gadobenate Dimeglumine Administration. Invest Radiol.2015;50(11):743-8. doi:10.1097/RLI.0000000000000206.
12. Ramalho J et al. High Signal in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR Images: Evaluation of Two Linear Gadolinium-based Contrast Agents. Radiology.2015;276(3):836-44.
13. Ramalho, J., Semelka, R.C. et al. Signal intensity change on unenhanced T1-weighted images in dentate nucleus following gadobenate dimeglumine in patients with and without previous multiple administrations of gadodiamide. Eur Radiol.2016;26:4080. DOI 10.1007/s00330-016-4269-7
14. Morcos SK, Extracellular gadolinium contrast agents: Differences in stability Eur J Radiol.2008;66:175–179
15. Huckle J et al, Gadolinium Deposition in Humans When Did We Learn That Gadolinium Was Deposited In Vivo? Invest Radiol.2016;51:236-40.
16. Baker J et al. Pharmacokinetics and Safety of the MRI Contrast Agent Gadoversetamide Injection (Optimark) in Healthy Pediatric Subjects. Invest Radiol.2004;39:334-39.
17. Wible J et al. Pharmacokinetics of gadoversetamide injection, a gadolinium-based contrast agent, in pediatric patients. Magn Reson Imaging.2009;27:512–18.

18. Pirovano G et al. Pharmacokinetics of Gadobenate Dimeglumine in Children 2 to 5 Years of Age Undergoing MRI of the Central Nervous System. J Magn Reson Imaging.2015;41:1096–103.
19. Hahn G et al. Pharmacokinetics and Safety of Gadobutrol-Enhanced Magnetic Resonance Imaging in Pediatric Patients. Invest Radiol.2009;44:776–83.
20. Kunze C, Mentzel HJ, Krishnamurthy R, et al. Pharmacokinetics and Safety of Macrocyclic Gadobutrol in Children Aged Younger Than 2 Years Including Term Newborns in Comparison to Older Populations. Invest Radiol.2016;51:50–57.
21. Scala M, Koob M, de Buttet S, Bourrinet P, Felices M, Jurkiewicz E. A. Pharmacokinetics, Efficacy, and Safety Study of Gadoterate Meglumine in Pediatric Subjects Aged Younger Than 2 Years. Invest Radiol. 2018 Feb;53(2):70-79.
22. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol.2009;20:629-37.
23. Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol.2009; 4(11):1832-43.
24. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol.2010;Nov;25(11):2321-6.
25. Hao J, Bourrinet P and Desché P. Assessment of pharmacokinetic, pharmacodynamic profile, and tolerance of gadopiclenol, a new high relaxivity GBCA, in healthy subjects and patients with brain lesions (phase I/IIa study): *Investigative Radiology*. 2019; 54: 396–402.
26. Bendszus M, Roberts D, Kolumban B, Meza JA, Bereczki D, San-Juan D, Liu BP, Anzalone N and Maravilla K,: Dose finding study of gadopiclenol, a new macrocyclic contrast agent, in MRI of central nervous system. *Invest Radiol* 2020;55: 129–137.
27. Funck-Brentano C., Felices M., Le Fur N., Dubourdieu C., Desché P., Vanhoutte F., and Voiriot P.: Randomized study of the effect of gadopiclenol, a new gadolinium-based contrast agent, on the QTc interval in healthy subjects. Br J Clin Pharmacol. 2020; 1–8.
28. Jurkiewicz E., Tsvetkova S, Grinberg A, Pasquiers B. Pharmacokinetics, Safety, and Efficacy of Gadopiclenol in Pediatric Patients Aged 2 to 17 Years. Invest Radiol. 2022; 57: 510-516.
29. Loevner LA, Kolumban B, Hutoczki G, et al. Efficacy and Safety of Gadopiclenol for Contrast-Enhanced MRI of the Central Nervous System: The PICTURE Randomized Clinical Trial. Invest Radiol. 2023;58(5):307-13.
30. Kuhl C, Csőszi T, Piskorski W, et al. Efficacy and safety of half-dose gadopiclenol versus fulldose gadobutrol for contrast-enhanced body MRI. Radiology. 2023 (in press).
31. Ross, R.D. The Ross Classification for Heart Failure in Children After 25 Years: A Review and an Age-Stratified Revision. Pediatr Cardiol 33, 2012; 1295–1300.

17 COMPANY LIABILITY INSURANCE

Guerbet's liability, as well as the liability of the Investigators participating to this trial, is covered by an insurance policy, a copy of the certificate being submitted to the Investigator.

Furthermore, Guerbet and the Investigator undertake to comply with the locally applicable legal requirements with respect to insurance.

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

- An accident due to a cause other than the investigational medicinal product administered,
- An accident occurring during use of the investigational medicinal product differently from the instructions given in the trial protocol,
- An accident occurring for a patient for whom parent(s) or legal guardian (where applicable) consent to participation was not adequately collected.

18 APPENDICES

Not applicable.