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Official Title	Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in pediatric patients from 2 to 17 years of age undergoing contrast-enhanced MRI
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Protocol No. GDX-44-007

Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in pediatric patients from 2 to 17 years of age undergoing contrast-enhanced MRI.

Phase II Clinical Trial

Design

Pharmacokinetics, open-label, uncontrolled, multicenter trial with age-staggered approach

[redacted]

EudraCT No.: 2018-001516-30

IND No.: 123673

COORDINATING INVESTIGATOR

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TRIAL SYNOPSIS

Trial Title: Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in pediatric patients from 2 to 17 years of age undergoing contrast-enhanced MRI. Phase II Clinical Trial	
Trial Product(s): [redacted]	Active Ingredient(s): gadopiclenol (P03277)
EudraCT No.: **2018-001516-30**	IND No.: 123673
Potential Participating countries (Potential Number of sites): Around 20 centers in approximately 5 European countries.	

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 from 2 to 17 years undergoing central nervous system (CNS) contrast-enhanced MRI (CNS cohort).

Secondary objectives:

1. To evaluate safety (clinical and biological) up to 3 months following single administration in both CNS and Body cohorts.
2. To evaluate urinary excretion of gadopiclenol quantitatively up to 8 hours and in subsequent urine samples collected up to 3 months following single administration in both CNS and Body cohorts (or exceptionally up to 4 months if collection is delayed due to the COVID-19 pandemic).
3. To evaluate efficacy of gadopiclenol -enhanced MRI for CNS and body 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 children aged from 2 to 17 years, using a population PK approach. This approach, allowing sparse blood sampling only is selected to minimize the clinical burden to children. Blood sampling will be performed via indwelling catheters rather than by repeated venipunctures. An optimized flexible design with 4 sampling windows (W) covering the first 8 hours following gadopiclenol injection will be used:

- W1: 1 min to 20 min
- W2: 30 min to 45 min
- W3: 2 to 3 hours
- W4: 7 to 8 hours

A total of 4 blood samples per patient will be taken post-injection for PK analysis, one within each window.

PK profile in plasma will only be investigated in the cohort of patients undergoing CNS contrast-enhanced MRI (CNS cohort).

Safety, urinary excretion and efficacy of gadopiclenol will be evaluated in both CNS cohort and in the cohort of patients undergoing contrast-enhanced MRI for diseases of other organs (Body cohort).

When possible, total urine over 8 hours will be quantitatively collected following gadopiclenol injection in patients capable to control daytime urination to evaluate the concentration of urinary

excreted gadopiclenol. An age-down staggered approach will be used. Patients will be recruited into 3 predefined age groups: 12-17, 7-11 and 2-6 years. The inclusions will start with the older group (Adolescents, 12-17 years), followed by Preadolescents (7-11 years) and finally Young Children (2-6 years of age).

The total sample size of 80 patients (60 in the CNS cohort and 20 in the Body cohort) will be balanced between 3 age groups as following:

- At least 15 patients and the number as close as possible to 20 patients will be included in each age group from the CNS cohort. The inclusion will be completed in parallel in all age groups to reach the overall number of 60 patients evaluable for the primary criterion.
- At least 3 patients from the Body cohort will be included per age group. The inclusion will be completed in parallel in all age groups to reach the overall number of 20 patients in the Body cohort.

The decision to start the next age group will be taken by Trial Safety Review Board (TSRB) based on safety assessment over one-day period after injection of the first 15 patients included in previous group from either CNS or both cohorts.

The previous age group will be completed in parallel with the start of the next group.

The children popPK model will be initiated with data from the first 15 patients in the adolescents' group from CNS cohort and will be continuously upgraded at each 15 subsequent completed patients in each of the following age groups from the same cohort.

Urine sampling to measure renal excretion of gadopiclenol will be performed 1 week and 3 months after gadopiclenol injection in patients with diseases in CNS and other body organs capable to control daytime urination. If the urine sampling is delayed at the visits V3-bis and V4-bis due to the COVID-19 pandemic it can take place up to 1 month and 4 months after gadopiclenol injection respectively.

Number of patients / sample size

The sample size of the CNS cohort was determined in order to optimize the characterization of gadopiclenol pharmacokinetics in pediatric population through population PK modelling. Sample size determination was coupled with PK sampling time optimization in order to determine the best possible design for the population PK modelling. The best design (in terms of sample size and sampling points) was defined as the design minimizing model's parameters root square error (RSE), hence providing the highest precision.

According to adult's data, a 2-compartment model with elimination from the central compartment described appropriately gadopiclenol pharmacokinetics. The design was evaluated for a sample size of 60 pediatric patients between 2 and 17 years old and predicted a correct estimation of all PK parameters.

The total sample size of 80 patients was estimated sufficient for the satisfactory exploration of safety and efficacy of gadopiclenol in pediatric patients with diseases of CNS and other organs.

Patient who has received an IMP injection and undergone an enhanced MRI examination in CNS without major deviations will be considered evaluable for the primary criterion.

Eligibility criteria

Inclusion criteria:

1. Female or male pediatric patient aged 2 to 17 years,
2. Patient with known or suspected lesion(s) scheduled to undergo routine contrast-enhanced MRI of CNS or of other organs including at least one organ among head and neck, thorax, abdomen, pelvis and musculoskeletal system (including extremities),

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 with capacity of understanding who received age- and maturity-appropriate information and provided his/her assent to participate in the trial (as required by national regulations),
5. 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 1 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 ranges [eGFR must be calculated based on bedside Schwartz equation],
4. Patients referred for MR Angiography.
5. Patient with history of bleeding disorder,
6. Patient with known severe liver disease,
7. Patient with known cardiac disease (e.g., heart rhythm anomalies, long QT syndrome),
8. Patient with any clinically significant abnormal 12-lead ECG that in the Investigator's opinion would affect the safety evaluation or place the patient at risk,
9. Patient with electrolyte or fluid imbalance that at Investigator's judgment presents undue risk assessed within 1 month prior to gadopiclenol administration,
10. Patient undergoing a change in chemotherapy within 1 day prior to or 1 day after gadopiclenol administration,
11. Patient who received or will receive any other contrast agent for CT and/or MRI within 1 week prior to or 1 week after gadopiclenol administration,
12. Patient with contraindication for MRI such as iron metal implants (e.g., aneurysm clips, pacemaker),
13. Patient with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents,
14. Patient with history of hypersensitivity caused by any contrast media / agents (iodinated or gadolinium-based),
15. Patient with known contraindication(s) to the use of any gadolinium-based contrast agent (GBCA),
16. Pregnant or breast-feeding female patient [female patient with childbearing potential (who experienced menarche) must have a negative urine pregnancy test within 24 hours prior to gadopiclenol administration and must be using medically approved contraception* if sexually active],
17. Patient with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate to the whole trial,
18. 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,

19. Having participated in a clinical trial and having received any investigational product within 7 days prior to gadopiclenol administration or planned during the trial,
20. Patient previously included in this trial,
21. Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

** medically approved contraception methods include: female sterilization, use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception, placement of an Intrauterine Device (IUD) or Intrauterine System (IUS), barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository).*

Investigational Medicinal Product administration

Trial product:

Name: gadopiclenol [redacted]

Pharmaceutical form: 20 ml vial of sterile, clear, ready-to-use aqueous solution for injection.

Concentration: 0.5 M

Route and method of administration:

The IMP will be administered intravenously (IV) as a bolus injection at a recommended rate of 1-2ml/sec. For dynamic contrast-enhanced studies the use of an injector is recommended. 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 with a normal 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). A qualified professional according to local regulation will be responsible for preparing the dosing solutions.

Trial duration for patients:

Expected trial duration for each patient is about 3 months:

Minimum trial duration for patients: 82 days
Maximum trial duration for patients: 111 days (up to 134 days in case V4-bis)

Each patient will undergo 4 visits:

- V1 - Screening: up to 14 days before inclusion;
- V2 - Inclusion: between D1 (gadopiclenol administration) and D2, including confinement period (if not prevented by the constraints linked to the COVID-19 pandemic);
- V3 – 1-week safety follow-up (followed by V3-bis: 1-month maximum safety follow-up if V3 was done by phone or video);
- V4 – 3-month safety follow-up (followed by V4-bis: 4-month maximum safety follow-up if V4 was done by phone or video);

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). 4 blood samples for pharmacokinetic analysis are collected within 4 sampling windows in the CNS cohort.

The patient participation starts from the signing of the Informed Consent Form at V1 (screening) and ends at V4 (3-month safety follow-up) or V4-bis (4-month maximum safety follow-up) when applicable or earlier in case of premature discontinuation.

Patients included and/or to be included in Body cohort may be impacted by COVID-19 pandemic related constraints. In this case following changes will be acceptable:

- V2-D1 – if 8 hour-confinement period cannot be respected, it may be shortened. The tasks or assessments planned up to 90 min after gadopiclenol injection are expected to be performed at site;
- V2-D2 - if the patient cannot come back to the site the investigator and other authorized trial staff are allowed to alternatively perform the visit at patient's home. If impossible, at the very least a phone or video call should be placed;
- V3 – at the very least a phone or video call followed by additional on-site visit (Visit 3-bis) no later than 30 days after the IMP injection; V4 – at the very least a phone or video call followed by additional on-site visit (Visit 4-bis) no later than 120 days after the IMP injection. In this case, maximum trial duration will be extended up to 134 days.

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 will be assessed in the CNS cohort both by age group and overall based on following pharmacokinetic parameters determined from the population PK model:
  - Simulated concentrations at 10, 20 and 30 minutes post injection
  - Area Under the Curve,
  - elimination half-life,
  - total clearance,
  - volume of distribution.

Secondary criteria:

Secondary criteria will be assessed in both CNS and Body cohorts.

- Clinical, biological and ECG safety
  - Vital signs (temperature, blood pressure, pulse rate and pulse oximetry), prior to IMP injection, 30-90 min after and 1 day after IMP injection,
  - 12-lead ECG recorded prior to IMP injection, 30-90 min after and 1 day after IMP injection. Heart rate, Intervals: RR, PR, QRS, QT, corrected QT (QTc Bazett and QTc Fridericia), ST segments, T-wave morphology, U-wave and global morphology will be analyzed,
  - 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 (eruption, extravasation and inflammation) at T0, 30-90 min after 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 (see Section 9.1.2 Collection and recording of adverse event),
- 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 undertaken.

- Gadopiclenol urine concentration will be measured in patients capable to control daytime urination:
  - in total urine quantitatively collected over 8 hours after gadopiclenol injection (or less if the confinement is not possible over this period due to the COVID-19 pandemic),
  - in spot urine samples 1 week and 3 months after gadopiclenol injection (or up to 1 month and 4 months after gadopiclenol injection if the urine sampling is delayed to visits V3-bis and V4-bis respectively due to the COVID-19 pandemic);
- Gadopiclenol-enhanced MRI (pre and pre+post comparison) efficacy evaluation in the CNS and Body cohorts will be performed by on-site radiologist based on following parameters:
  - Technical adequacy for diagnosis using a 4-point scale;
  - Assessment of contrast quality: percentage of enhancement (E%) and Lesion to Background Ratio (LBR) for up to 3 most representative lesions;
  - Lesion visualization (lesion border delineation, internal morphology and contrast enhancement) using a 4-point scale for each parameter;
  - Change in diagnostic confidence following gadopiclenol administration.

Statistical methods

Descriptive statistical analysis for pharmacokinetic profile in plasma, urine excretion, clinical and biological safety and gadopiclenol-enhanced MR efficacy evaluation.

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).

TRIAL FLOW CHART

Time points Evaluation/procedures	V1	V2							V3[11]	V4[12]
	Screening visit	Inclusion Visit 1-day confinement period[1]							1-week safety follow-up	3-month safety follow-up
	-14 days to	D1						D2[10]	D8	D90
			T0	W1	W2	W3	W4			
		Prior to IMP injection	IMP injection	1 - 20 min	30 - 45 min	2 - 3 h	7 - 8 h	1 day	7 ± 1 days	3 months ± 7 days
Eligibility criteria	X	X								
Informed consent signature	X									
Patient number assignment	X									
Demographic data	X	X								
Medical/surgical history	X									
Physical examination[2]	X							X	X	X
Vital signs (temperature, blood pressure, pulse rate and pulse oximetry)		X			X[3]			X		
Body weight and height		X								
Cardiac rhythm (12 lead ECG)		X			X[3]			X		
Concomitant treatments[4]	←								→	X[4]
Pregnancy test for female patient with childbearing potential		X								
Blood sampling for biochemistry and hematology	X[5]							X		
eGFR (bedside Schwartz equation)	X[6]							X		
IMP allocation via IWRS		X								
IMP administration			X							
MRI		X	X	X[7]	X[7]					
Non-serious AE[8]	←								→	X[8]
SAE and AESI[8]	←									→
Injection site tolerance			X		X[3]			X		
Blood sampling for PK analyses (for CNS cohort only)				X	X	X	X			
Urine sampling for the IMP concentration[9]			←				→		X	X

(1) Confinement period can be reduced to 8 hours after the injection if patient remains close to the site and can easily come back for the D2 visit. In case of COVID-19 pandemic related constraints, if the 8 hours confinement period cannot be respected, it may be shortened. The tasks or assessments planned up to 90min after Gadopiclenol injection are expected to be performed at site

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

(3) Vital signs, Injection site tolerance and ECG will be evaluated within the time window W2 and up to 90 min after gadopiclenol injection.

(4)Any medication, including homeopathic products, over-the-counter medications, as well as prescription drugs, on-going at D1 or administered until 1-week safety visit (D8) will be recorded in the patient's eCRF. The concomitant medications/treatments started from D2 to D8 will be documented if the patient experienced at least one AE.

Between D8 and D90 safety visits, any GBCA injection will be documented. Other concomitant medications/treatments will be documented if it is corrective treatment related to the reported AE.

(5) At screening, blood sample will be collected to analyse biochemistry and hematology in central lab and to measure serum creatinine. In order to enable the eligibility criteria assessment prior to MRI, sCr can be assessed locally as well.

(6) At screening, locally or centrally calculated eGFR will be used to verify the non-inclusion criterion and centrally calculated eGFR will be used to assess safety. The height used for the local calculation must be specified in the source data along with the creatinine measured locally.

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

(8) All Adverse Events occurring from the beginning of the patient's participation in the trial (Informed Consent Form signature) and until 1-week safety visit (D8 or the day of Visit 3-bis), 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 according to Investigator's opinion. Non-serious AEs occurring after 1-week safety visit (D8) must be reported if related to the drug or to the trial and followed until recovery or sequelae stabilization.

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 3-month safety visit (D90 or the day of Visit 4-bis) must be reported and followed until recovery or sequelae stabilization (see Section 9.1.2).

(9) Due to COVID-19 pandemic related constraints, patients included in Body cohort may not be allowed to stay at hospital for the full 8 hour-period. In this case the total urine collection will end when the patient is discharged from the hospital.

(10) In case of COVID-19 pandemic related constraints, data collection at D2 will be insured as far as possible at site or at patient's home by the investigating staff. At the very least a phone or video call will be placed to remotely enquire about new AE, follow up on previously reported AE, injection site

tolerance (eruption, extravasation and inflammation), any change in on-going medications/treatments and new concomitant medications/treatments.

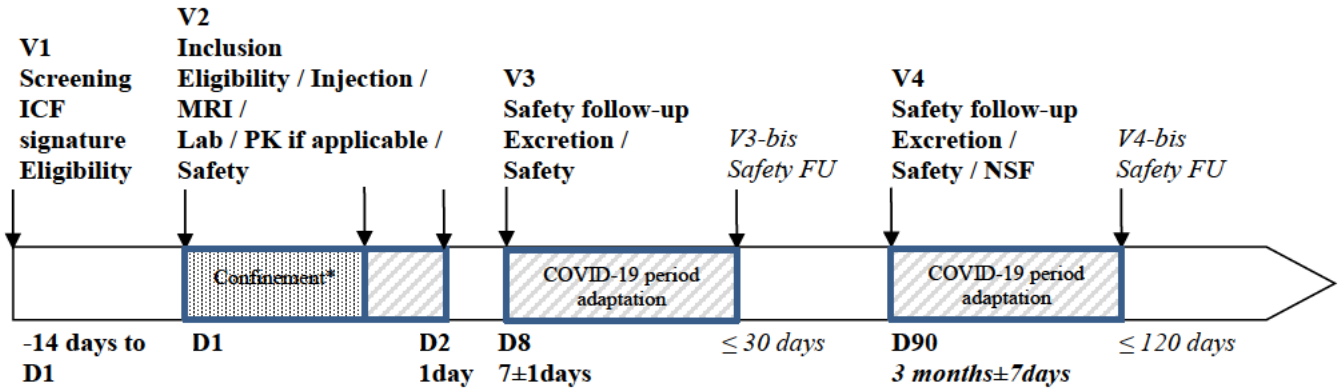
(11) In case of COVID-19 pandemic related constraints, data collection at V3 will be insured as far as possible. At the very least a phone or video call will be placed to remotely enquire about new AE, follow up on previously reported AE, any change in on-going medications/treatments since last visit and new concomitant medications/treatments if the patient experienced at least one AE.

In case of remote Visit 3, an additional on-site visit (Visit 3-bis) should be scheduled whenever possible at the earliest possible timepoint and no later than 30 days after the IMP injection. All tasks or assessments planned for the Visit 3 at site will be performed during Visit 3-bis.

(12) In case of COVID-19 pandemic related constraints, data collection at V4 will be insured as far as possible. At the very least a phone or video call will be placed to remotely enquire about new non-serious AE related to the drug or to the trial, SAE and AESI since the last visit, follow up on previously reported AE, any GBCA injection since the last visit and other concomitant medications/treatments if related to the reported AE.

In case of remote Visit 4, an additional on-site visit (Visit 4-bis) should be scheduled whenever possible, at the earliest possible timepoint and no later than 120 days after the IMP injection. All tasks or assessments planned for the Visit 4 at site will be performed during Visit 4-bis.

TRIAL DIAGRAM



Expected minimum trial duration for each patient: 82 days

Expected maximum trial duration for each patient: 111 days (up to 134 days in case V4-bis)

*Under certain conditions, confinement period can be reduced to 8 hours.

SIGNATURE PAGE

GUERBET MEDICAL EXPERT [redacted]	Signature: Date:
GUERBET CLINICAL PROJECT MANAGER [redacted]	Signature: Date:
GUERBET BIOSTATISTICIAN [redacted]	Signature: Date:

COORDINATING INVESTIGATOR [redacted]	Signature: Date:

"Due to current sanitary conditions, wet ink signatures are temporarily replaced by electronic sign-off. Original signatures will be collected when permitted and document sent upon request. [March 20, 2020]".

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
AESI	Adverse Event of Special Interest
Body cohort	Patients undergoing contrast-enhanced MRI for diseases of other than CNS organs
BW	Body Weight
CNS cohort	Patients undergoing CNS contrast-enhanced MRI
CRA	Clinical Research Associate (syn. Monitor)
CRF/eCRF	Case Report Form/ electronic Case Report Form
CT	Computed Tomography
ECG	Electrocardiography
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIM	Fisher Information Matrix
GBCA	Gadolinium-based contrast agent
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMS	Isotope Dilution Mass Spectroscopy
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
IWRS	Interactive Web Response System
LBR	Lesion to Background Ratio
MRI	Magnetic Resonance Imaging
PC-AKI	Post-contrast acute kidney injury
PK	Pharmacokinetic/Pharmacokinetics
PPS	Per Protocol Set
RSE	Root Square Error
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
sCr	Serum Creatinine
SD	Standard deviation
SOP	Standard Operating Procedure
SPC/SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TSRB	Trial Safety Review Board
W	Window

TABLE OF CONTENTS

LIST OF FIGURES

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1. INTRODUCTION AND 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 (eg, 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 [1].

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 relaxivity, 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 [2-6].

However, gadobenate dimeglumine is belonging to linear GBCAs, and some of the recently published studies showed gadolinium retention in the brain related to linear agents [7-12] even though clinical consequence of this finding is still under investigation. However, gadolinium retention raise special concern in the potentially vulnerable pediatric patient population. There is thus a medical need to have a macrocyclic agent with a high relaxivity for diagnosing and monitoring a wide range of childhood diseases.

Gadopiclenol (P03277) is a new paramagnetic, macrocyclic, non-ionic GBCA developed for intravenous (IV) use during MRI. Its molecular weight is 970.11 g/mol [redacted].

[redacted]

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 relaxivity compared to other available GBCAs including gadobenatedimeglumine 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.

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 [13]. Therefore 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 [14]. Therefore a good long-term safety is anticipated.

Several published studies documented the pharmacokinetic profiles of GBCAs in children. All patients 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 [15-20]. The trial will analyze the PK profiles of gadopiclenol after a single injection of 0.05 mmol/kg BW, a half as high as dosage of other GBCAs used in children. Based on preliminary data in adults this dosage is expected to provide satisfactory efficacy.

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

At the time of this protocol submission, the following clinical data in adults 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. 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.

For the phase I trial, six intravenous doses ranged 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 dose-independent. The elimination half-life of gadopiclenol ranged from 1.5 to 2 hours and urinary excretion in the unchanged form showed to be the major route of elimination for gadopiclenol.

For the Phase IIa trial, 4 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 of them underwent MRI examination. Similar gadopiclenol concentrations and pharmacokinetics were observed in patients versus healthy subjects at corresponding doses. One SAE not related to gadopiclenol was reported (see Investigator Brochure for detailed information).

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

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

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 BW and 0.3 mmol/kg BW) with positive control. Urinary and blood long term elimination was evaluated up to 3 months after the injection. The trial demonstrated that gadopiclenol did not prolong the QT interval neither at the dose of 0.1 mmol/kg nor at the dose of 0.3 mmol/kg in healthy volunteers. The clinical and biological safety profile of the product observed during the study did not raise any concern.

Another trial is ongoing without safety concerns having been raised so far.

Phase I trial in patients with renal insufficiency (GDX-44-005) is designed to include 5 successive cohorts of 8 subjects: volunteers and patients with mild, moderate, severe and end stage renal disease. Urinary and blood long term elimination will be evaluated up to 6 months following gadopiclenol IV injection at a dose of 0.1 mmol/kg BW.

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

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 from 2 to 17 years undergoing central nervous system (CNS) contrast-enhanced MRI (CNS cohort).

2.2 Secondary Objectives

1. To evaluate safety (clinical and biological) up to 3 months following single administration in both CNS and Body cohorts.
2. To evaluate urinary excretion of gadopiclenol quantitatively up to 8 hours and in subsequent urine samples collected up to 3 months following single administration in both CNS and Body cohorts (or exceptionally up to 4 months if collection is delayed due to the COVID-19 pandemic).
3. To evaluate efficacy of gadopiclenol-enhanced MRI for CNS and body as assessed by on-site Investigator.

2.3 Sub-Trial / Ancillary Trial Objectives

Not applicable.

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 children aged from 2 to 17 years, using a population PK approach. This approach, allowing 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 was used to optimize the trial design and PK sampling time.
Blood sampling will be performed via indwelling catheters rather than by repeated venipunctures. An optimized flexible design with 4 sampling windows (W) covering the first 8 hours (at least 4 elimination half-lives of gadopiclenol following the injection will be used:

- W1: 1 min to 20 min
- W2: 30 min to 45 min
- W3: 2 to 3 hours
- W4: 7 to 8 hours

A total of 4 blood samples per patient will be taken post-injection for PK analysis, one within each window.

PK profile in plasma will only be investigated in the cohort of patients undergoing CNS contrast-enhanced MRI (CNS cohort). Safety, urinary excretion and efficacy of gadopiclenol will be evaluated in both CNS cohort and in the cohort of patients undergoing contrast-enhanced MRI for diseases of other organs (Body cohort).

When possible, total urine over 8 hours will be quantitatively collected following gadopiclenol injection in patients capable to control daytime urination to evaluate the concentration of urinary excreted gadopiclenol.

An age-down staggered approach will be used. Patients will be recruited into 3 predefined age groups: 12-17, 7-11 and 2-6 years. The inclusions will start with the older group (Adolescents, 12-17 years), followed by Preadolescents (7-11 years) and finally Young Children (2-6 years).

The total sample size of 80 patients (60 in the CNS cohort and 20 in the Body cohort) will be balanced between 3 age groups as following:

- At least 15 patients and the number as close as possible to 20 patients will be included in each age group from the CNS cohort. The inclusion will be completed in parallel in all age groups to reach the overall number of 60 patients evaluable for the primary criterion.
- At least 3 patients from the Body cohort will be included per age group. The inclusion will be completed in parallel in all age groups to reach the overall number of 20 patients in the Body cohort.

The decision to start the next age group will be taken by Trial Safety Review Board (TSRB) based on safety assessment over one-day period after injection of the first 15 patients included in previous group from either CNS or both cohorts. The previous age group will be completed in parallel with the start of the next group (Figure 2).

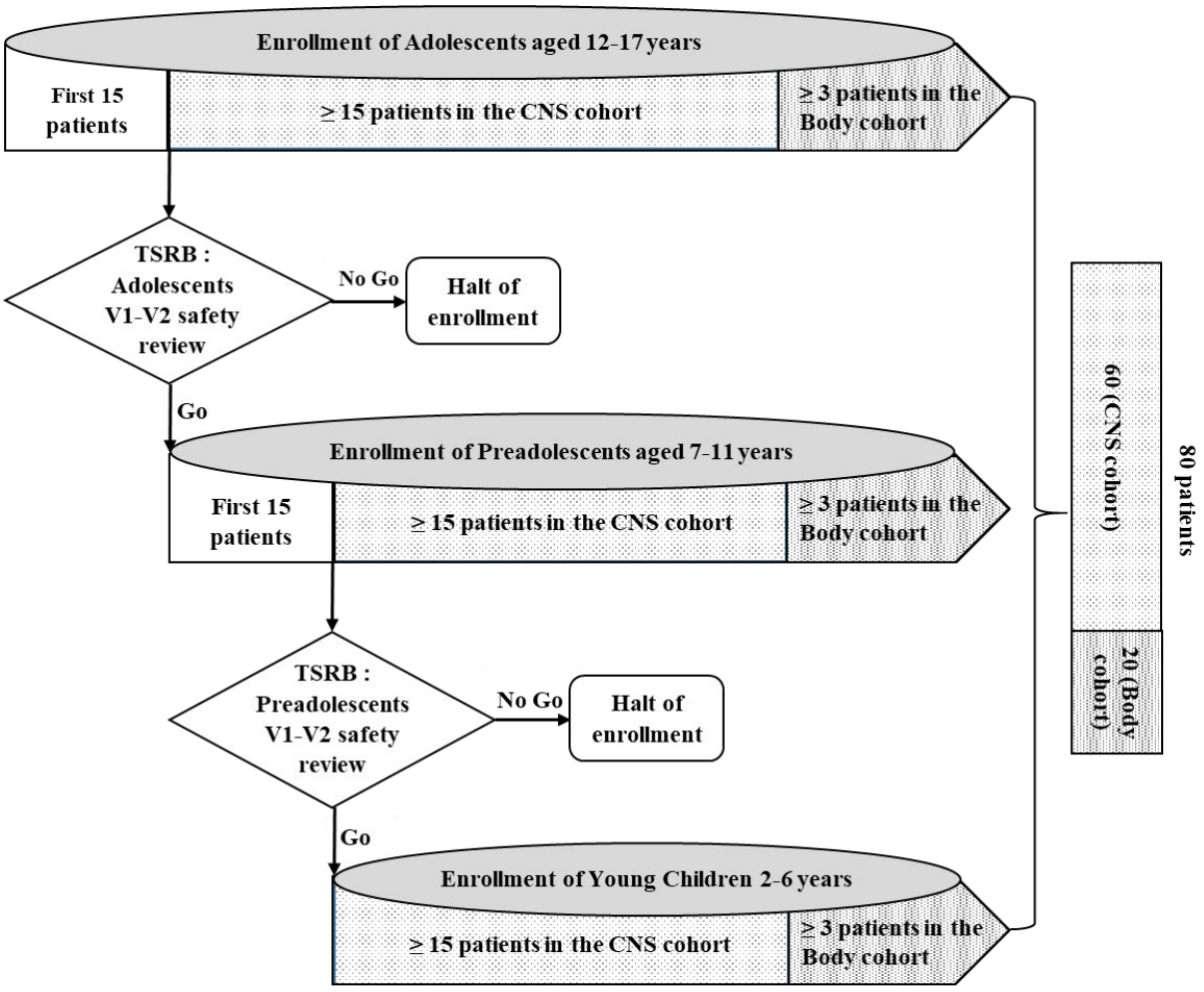
The children popPK model will be initiated with data from the first 15 patients in the adolescents' group from the CNS cohort and will be continuously upgraded at each 15 completed patients from the same cohort in each of the following age groups to simulate expected exposure.

Any patient who has received an IMP injection and undergone an enhanced MRI examination in CNS without major deviations, will be considered evaluable for the primary criterion.

Urine sampling to assess potential long term excretion of gadopiclenol, by measuring concentration of gadopiclenol, will be performed 1 week and 3 months after gadopiclenol injection in patients with diseases in CNS and other body organs capable to control daytime urination. If the urine sampling is

delayed at the visits V3-bis and V4-bis due to the COVID-19 pandemic it can take place up to 1 month and 4 months after gadopiclenol injection respectively.

Figure 2: Age-down staggered enrollment



3.2 Trial Duration

Each patient will undergo 4 visits:

- V1 - Screening: up to 14 days before inclusion;
- V2 - Inclusion: between D1 (gadopiclenol administration) and D2, including confinement period (if not prevented by the constraints linked to the COVID-19 pandemic);
- V3 – 1-week safety follow-up (followed by V3-bis: 1-month maximum safety follow-up if V3 was done by phone or video);
- V4 – 3-month safety follow-up (followed by V4-bis: 4-month maximum safety follow-up if V4 was done by phone or video);

Patient eligibility is appraised at screening visit and takes place up to 14 days before inclusion. The screening visit can be performed the same day as V2 if 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), and blood samples for pharmacokinetic analysis in CNS cohort are collected within 4 sampling windows (W) covering the first 8 hours following gadopiclenol injection:

- W1: 1 min to 20 min
- W2: 30 min to 45 min
- W3: 2 to 3 hours
- W4: 7 to 8 hours

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

Minimum trial duration for each patient: 82 days

Maximum trial duration for each patient: 111 days (up to 134 days in case of V4-bis)

Patient participation starts from the signing of the Informed Consent Form at V1 (screening) and ends at V4 (3-month safety follow-up) or V4-bis (4-month maximum safety follow-up) or earlier in case of premature discontinuation.

Patients included and/or to be included in Body cohort may be impacted by COVID-19 pandemic related constraints. In this case following changes will be acceptable:

- V2-D1 – if 8 hour-confinement period cannot be respected, it may be shortened. The tasks or assessments planned up to 90 min after gadopiclenol injection are expected to be performed at site;
- V2-D2 – if the patient cannot come back to the site the investigator and other authorized trial staff are allowed to alternatively perform the visit at patient's home. If impossible, at the very least a phone or video call should be placed
- V3– at the very least a phone or video call followed by additional on-site visit (Visit 3-bis) no later than 30 days after the IMP injection;
- V4 – at the very least a phone or video call followed by additional on-site visit (Visit 4-bis) no later than 120 days after the IMP injection. In this case, maximum trial duration will be extended up to 134 days.

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.

3.3 Interim Analysis

Not applicable.

3.4 Trial Committee(s)

Trial Safety Review Board (TSRB) described in Section 12 is established for:

- assessing the safety data at intervals and to decide whether to continue, modify, or stop the trial;
- taking a decision to start the enrollment of the next age down group based on the safety assessment in the previous groups (Adolescents and Preadolescents).

4. PATIENT SELECTION

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 2 to 17 years,
2. Patient with known or suspected lesion(s) scheduled to undergo routine contrast-enhanced MRI of CNS or of other organs including at least one organ among head and neck, thorax, abdomen, pelvis and musculoskeletal system (including extremities),
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 with capacity of understanding who received age- and maturity-appropriate information and provided his/her assent to participate in the trial (as required by national regulations),
5. Patient affiliated to national health insurance according to local regulatory requirements.

4.2 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 1 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 ranges [eGFR must be calculated based on bedside Schwartz equation],
4. Patients referred for MR Angiography.
5. Patient with history of bleeding disorder,
6. Patient with known severe liver disease,
7. Patient with known cardiac disease (e.g., heart rhythm anomalies, long QT syndrome),
8. Patient with any clinically significant abnormal 12-lead ECG that in the Investigator's opinion would affect the safety evaluation or place the patient at risk,
9. Patient with electrolyte or fluid imbalance that at Investigator's judgment presents undue risk assessed within 1 month prior to gadopiclenol administration,
10. Patient undergoing a change in chemotherapy within 1 day prior to or 1 day after gadopiclenol administration,
11. Patient who received or will receive any other contrast agent for CT and/or MRI within 1 week prior to or 1 week after gadopiclenol administration,
12. Patient with contraindication for MRI such as iron metal implants (e.g., aneurysm clips, pacemaker),
13. Patient with history of anaphylactoid or anaphylactic reaction to any allergen including drugs,
14. Patient with history of hypersensitivity caused by any contrast media / agents (iodinated or gadolinium-based),
15. Patient with known contraindication(s) to the use of any gadolinium-based contrast agent (GBCA),
16. Pregnant or breast-feeding female patient [female patient with childbearing potential (who experienced menarche) must have a negative urine pregnancy test within 24 hours prior to gadopiclenol administration and must be using medically approved contraception* if sexually active],

17. Patient with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate to the whole trial,
18. 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,
19. Having participated in a clinical trial and having received any investigational product within 7 days prior to gadopiclenol administration or planned during the trial,
20. Patient previously included in this trial,
21. Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct.

** medically approved contraception methods include: female sterilization, use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception, placement of an Intrauterine Device (IUD) or Intrauterine System (IUS), barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository).*

4.3 Patient Identification

After having obtained the written informed consent and verified that all eligibility criteria are met, Patients will be enrolled in the trial and will be allocated a unique Identification Number (Patient ID).

This Patient ID will contain 8 digits: the first three digits corresponding to the country number, 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 enrollment. The lowest enrollment number will correspond to the first patient enrolled at this site and the highest number to the last patient enrolled.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

Investigational Medicinal Product(s) 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 and Administration Modalities

Gadopiclenol [redacted] is a sterile, clear, ready-to-use aqueous solution for injection contained in vials of 20 ml, concentrated at 0.5 M

Gadopiclenol is administered intravenously (IV) as a bolus injection at a recommended rate of 1-2 ml/sec. For dynamic contrast-enhanced studies the use of an injector is recommended. 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 with a normal 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.

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 should receive added surveillance (e.g., carefully monitored pulse and blood pressure).

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 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). A qualified professional according to local regulation (study nurse or technician) will be responsible for preparing the dosing solutions.

Patients will receive a single dose of gadopiclenol on the day of MRI examination at T0.

For more information on gadopiclenol please refer to the Investigator 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.

IMP will consist in a box that contains one 20 ml vial 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 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.

5.3 Condition of Investigational Medicinal Product Allocation

5.3.1 Investigational Product(s) Allocation / Randomization

A central web randomization system or IWRS (Interactive Web Response System) will be used to manage inclusion of patients in the trial 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: Adolescents (12-17 years), Preadolescents (7-11 years) and Young Children (2-6 years).

Although a total number of 20 patients evaluable for the primary criterion (CNS cohort) is targeted in each age group, a slight imbalance between the groups is acceptable with a minimum of 15 patients in each age group and a maximum of 25 in the group with quicker enrollment in order to facilitate the inclusion of the last 5 patients.

At least 3 patients from the Body cohort will be included per age group.

First enrollment in the next age group will be conditioned by the decision of the TSRB. The inclusion will continue until the overall number reaches 60 patients evaluable for the primary criterion in the CNS cohort and 20 patients included in the Body cohort.

IMP number will be independent from the Patient Identification Number.

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, etc.) should be promptly notified to GUERBET, who will initiate a complaint procedure.

Under no circumstances shall the Investigator supply IMP to a third party, 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(s) and Other Trial Products

Not applicable.

5.6 Trial Product(s) Compliance and Accountability

The Investigator, the hospital pharmacist, or other allowed personnel will keep accurate records of Investigational Medicinal Products accountability at site level as well as accurate records of the batch numbers and quantities of the IMP given to each patient.

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

6. CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

Any medication, including homeopathic products, over-the-counter medications, as well as prescription drugs, on-going at D1 or administered until 1-week safety visit (D8) will be recorded in the patient's eCRF. The concomitant medications/treatments started from D2 to D8 will be documented if the patient experienced at least one adverse event.

Between D8 and D90 safety visits, any GBCA injection will be documented. Other concomitant medications/treatments will be documented if it is a corrective treatment related to the reported AE.

The following information must be provided:

- Drug (brand name or generic name)
- Route of administration
- Purpose (medical history/AE/pre-medication/contraception/prophylaxis)
- Indication
- Start/end of treatment

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 is capable of preventing 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.

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 should be encouraged to drink water and other non-alcoholic fluids liberally before and after the injection.

According to current knowledge, there is no other concomitant treatment of special attention 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 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 prohibited 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 will be assessed in the CNS cohort both by age group and overall based on following pharmacokinetic parameters determined from the population PK model:

- Simulated concentrations at 10, 20 and 30 minutes post injection
- Area Under the Curve,
- elimination half-life,
- total clearance,
- volume of distribution.

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

A separate analytical protocol will describe the gadopiclenol assays in plasma and urine samples. [redacted]

7.2 Secondary Criteria

Secondary criteria will be assessed in both CNS and Body cohorts.

7.2.1 Clinical, biological and ECG safety data

- Vital signs (temperature, systolic and diastolic blood pressure, pulse rate and pulse oximetry), prior to IMP injection, 30-90 min after and 1 day after IMP injection,

  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.

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

- 12-lead ECG recorded prior to IMP injection, 30-90 min after and 1 day after IMP injection.
  - Heart rate
  - Intervals: RR, PR, QRS, QT [corrected QT (QTc) will be calculated according to Fridericia and Bazett methods]
  - ST segments, T-wave morphology, U-wave
  - Global morphology

  ECG will be recorded after a rest for at least 5 minutes in supine position. A notable QTc change is defined as a QTc (Fridericia's or Bazett's) interval > 450 ms for males and females or an increase of >30 ms from baseline. All ECGs changes considered as abnormal and clinically significant according to Investigator's judgment will be reported as AEs.

- Safety laboratory variables centrally analyzed (hematology and biochemistry) from blood samples collected prior to 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, glucose, blood urea nitrogen (BUN), creatinine, total protein, calcium, phosphorus, 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) centrally calculated based on the bedside Schwartz equation prior to and 1 day after IMP injection,

  Bedside Schwartz equation [21-23] is 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.

- Tolerance at the injection site (eruption, extravasation and inflammation) at T0, 30-90 min after 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 (see Section 9.1.2).

- Clinical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit (or 4-month follow-up safety visit in case of V4-bis).

  Following symptoms will be recorded: 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 be undertaken and results reported to the eCRF.

7.2.2 Gadopiclenol urine concentration

Gadopiclenol urine concentration will be measured in patients capable to control daytime urination:

- in total urine quantitatively collected over 8 hours after gadopiclenol injection (or less if the confinement is not possible over this period due to the COVID-19 pandemic)

- in spot urine samples 1 week and 3 months after gadopiclenol injection (or up to 1 month and 4 months after gadopiclenol injection if the urine sampling is delayed to visits V3-bis and V4-bis respectively due to the COVID-19 pandemic).

7.2.3 Gadopiclenol-enhanced MRI (pre and pre+post comparison) efficacy evaluation in the CNS and Body cohorts by on site radiologist

- Technical adequacy for diagnosis using a 4-point scale: nondiagnostic, poor, fair and good.

- Assessment of contrast quality: percentage of enhancement (E%) and Lesion to Background Ratio (LBR): for up to 3 most representative lesions.
    - Measurements of the signal intensity (SI) of the lesion will be performed on the pre and post-injection identical T1 weighted sequences.
    - Measurements of the SI of background tissue (SI_b) will be performed on post-injection T1 weighted sequence.
    - Measurements of the SI of the lesion are to be made on the best representative images of the pathology. These images will be selected according to the following:
        - Up to 3 most representative lesions (largest enhancing lesion) will be measured separately,
        - The ROI for a lesion will encompass a homogeneous area within the lesion as large as possible.
    - Measurements of the background tissue's SI are to be placed in the target region on the slice where corresponding lesion is located. The ROI should be as large as possible.

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

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

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

SI_{pre} = SI of lesion on pre injection images.

Lesion to Background Ratio (LBR) will be calculated by using the equations below:

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

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

SI_b = SI of background (surrounding healthy tissue of the lesion) on post injection images.

- Lesion visualization (lesion border delineation, internal morphology and contrast enhancement) assessed using a 4-point scale for each parameter.
The Investigator will record each of lesion visualization variables (lesion border delineation, internal morphology and degree of contrast enhancement) for up to 3 most representative enhancing lesions.

    - Border delineation:

    Delineation of the lesion border is defined as the distinction of lesion from surrounding tissues, structures, or edema; and the detection of extent of the lesion (for extra-axial lesions, this pertains to the definition of the space in which the lesion is present, and for intra-axial lesions, it pertains to the invasion of white matter, gray matter, or both; the neuroanatomical distribution of the lesion; and its mass effect). This criterion will be assessed through the following scale:

        - 1 = none: no or unclear delineation
        - 2 = moderate: some areas of clear delineation but also with some significant areas of non-distinct delineation

- 3 = good: almost clear but not complete delineation
- 4 = excellent: border outline is sharp with clear and complete delineation

- Internal morphology:

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

- 1 = poor: poorly seen
- 2 = moderate: majority of lesion is poorly seen but with minor parts of lesion visible
- 3 = good: majority of lesion is clearly seen but with minor parts of lesion invisible
- 4 = excellent: lesion is well seen and can see "through" lesion to observe any complex areas of necrosis or hemorrhage or cyst formation.

- Degree of contrast enhancement:

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

- 1 = no: no enhancement
- 2 = moderate: weakly enhanced
- 3 = good: clearly enhanced
- 4 = excellent: clearly and brightly enhanced

- Change in diagnostic confidence: following gadopiclenol administration, the Investigator's diagnostic confidence is improved or remains unchanged or getting worse.

8. TRIAL SCHEDULE AND PROCEDURES

8.1 Trial Schedule

Day 1 is defined as the day of IMP injection.

8.1.1 Screening – Visit 1 – Day - 14 to Day 1

During this visit, the following tasks or assessments will be performed in patients from both CNS and Body cohorts:

- The patient with capacity of understanding will receive age- and maturity-appropriate information about his/her participation in the trial and his/her assent to participate in the trial will be obtained (as required by national regulations);
- Written informed consent for the participation of the child in the trial prior to any trial related procedure will be obtained from parent(s) or legal guardian (where applicable) as described in Section 13.3;
- Verification of all eligibility (inclusion/non-inclusion) criteria will be done by the Investigator;
- The patient will be attributed an Identification Number in chronological order;
- Demographic data will be recorded: sex, race/ethnicity and age (years and months);
- Medical/Surgical history and current medical condition will be obtained. The Investigator will question on any possible previous contrast agents injection (type of contrast agent injected and tolerance will be recorded);
- A physical examination will be performed. Physical examination will include: general appearance, skin, neck (including thyroid), eyes, ENT (ears, nose, throat), lungs, heart, abdomen, back, lymph nodes, extremities, peripheral vascular and neurological examination;
- Medications and treatments on-going at the time of signing informed consent will be documented;
- Blood sample will be collected and analyzed :
  - In Local or Central Lab for serum creatinine measurement. The result must be available at the time of the inclusion and will be used to estimate glomerular filtration rate (eGFR) for the inclusion criterion. eGFR will be calculated based on the bedside Schwartz equation.
  - In Central Lab:
    - 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, glucose, blood urea nitrogen (BUN), creatinine, total protein, calcium, phosphorus, total bilirubin, conjugated bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate

dehydrogenase (LDH), PT (prothrombin time) / INR (International Normalised Ratio).

8.1.2 Inclusion – Visit 2 – From Day 1 to Day 2

Patients will be hospitalized for a confinement period of 1 day. Confinement period can be reduced to 8 hours after the injection if patient remains close to the site and can easily come back for the D2 visit. Images acquisition before and after gadopiclenol injection will be performed according to the Imaging Manual. Diagnostic will be recorded. Total urine will be collected over 8 hours after the injection to measure concentration of the urinary excreted gadopiclenol in patients capable to control daytime urination.

Due to COVID-19 pandemic related constraints, patients included in Body cohort may not be allowed to stay at hospital for the full 8 hour-period. In this case the total urine collection will end when the patient is discharged from the hospital. Actual duration of total urine collection will be recorded. The tasks or assessments planned up to 90 min after gadopiclenol injection are expected to be performed at site.

8.1.2.1 Day 1

Throughout the Day 1, the following other tasks or assessments will be performed in patients from both cohorts:

8.1.2.1.1 Prior to gadopiclenol injection

- Verification of all eligibility (inclusion/non-inclusion) criteria will be done by the Investigator;
- Indication for current contrast-enhanced MRI will be recorded;
- Demographic data will be recorded: age (years and months);
- Other baseline characteristics will be recorded: childbearing potential for female patient (experienced menarche) and ability to control daytime urination;
- Vital signs (temperature, blood pressure, pulse rate and transcutaneous non-invasive pulse oximetry using a light emitter) will be measured;
- Body weight and height will be measured;
- Standard 12-lead electrocardiogram (ECG) will be recorded and assessed;
- Any change in on-going or new medication and treatment since last visit will be documented;
- Urine pregnancy test will be performed for female patient with childbearing potential;
- AEs occurred since screening visit will be recorded and assessed.

8.1.2.1.2 Time point T0

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

- Injection site tolerance (eruption, extravasation and inflammation) will be evaluated and any event will be reported as adverse event in patients from both cohorts;
- Start of total urine collection over 8 hours in patients from both cohorts capable to control daytime urination.

8.1.2.1.3 Time window W1

The following task will be performed within first time window (1-20 min) after gadopiclenol injection:

- Blood sample will be collected for PK analysis in patients from the CNS cohort. Actual sampling time must be recorded;

8.1.2.1.4 Time window W2

The following task will be performed within second time window (30-45 min) after gadopiclenol injection:

- Blood sample will be collected for PK analysis in patients from the CNS cohort. Actual sampling time must be recorded.

The following tasks or assessments will be performed within W2 and up to 90 min after gadopiclenol injection in patients from both cohorts:

- Vital signs (temperature, blood pressure, pulse rate and transcutaneous non-invasive pulse oximetry using a light emitter) will be measured;
- Injection site tolerance (eruption, extravasation and inflammation) will be evaluated and any event will be reported as adverse event;
- Standard 12-lead ECG will be recorded and assessed;

8.1.2.1.5 Time window W3

The following task will be performed within third time window (2-3h) after gadopiclenol injection:

- Blood sample will be collected for PK analysis in patients from the CNS cohort. Actual sampling time must be recorded.

8.1.2.1.6 Time window W4

The following task will be performed within fourth time window (7-8h) after gadopiclenol injection:

- Blood sample will be collected for PK analysis in patients from the CNS cohort. Actual sampling time must be recorded.

8.1.2.1.7 Time point T8h

- End of total urine collection in patients from both cohorts capable to control daytime urination.

8.1.2.2 Day 2

The following tasks or assessments will be performed 1 day after gadopiclenol injection in patients from both cohorts:

- A physical examination will be performed.

- Vital Signs (temperature, blood pressure, pulse rate and transcutaneous non-invasive pulse oxymetry using a light emitter) will be measured;
- Standard 12-lead ECG will be recorded and assessed;
- Blood sample will be collected and following laboratory parameters will be analysed in the Central Lab:
  - 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, glucose, blood urea nitrogen (BUN), creatinine, total protein, calcium, phosphorus, 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 based on the Bedside Schwartz equation;
- Injection site tolerance (eruption, extravasation and inflammation) will be evaluated and any event will be reported as adverse event;
- Any change in on-going medication and treatment since Day 1 will be documented. New concomitant medications/treatments will be documented if the patient experienced at least one AE;
- All AEs occurred since Day 1-T0 will be recorded and assessed.

If it is not possible to perform the corresponding assessments on site due to COVID-19 pandemic related constraints, the investigator and other authorized trial staff are allowed to alternatively perform the visit at patient's home to insure data collection as far as possible. If this option is also impossible, at the very least a phone or video call should be performed by investigator to ensure follow-up of patient's safety and remotely enquire about:

- New AE occurred since Day 1-T0;
- Follow up on previously reported AE;
- Injection site tolerance (eruption, extravasation and inflammation) will be evaluated and any event will be reported as adverse event;
- Any change in on-going medication and treatment since Day 1;
- New concomitant medications/treatments.

8.1.3 Safety Follow-up – Visit 3 – Day 8

During this visit, the following tasks or assessments will be performed in patients from both cohorts:

- A physical examination will be performed;
- Any change in on-going medication/treatment since last visit will be documented. Other new concomitant medications/treatments will be documented if the patient experienced at least one AE;
- Spot urine sample will be collected to measure concentration of the excreted gadopiclenol in patients capable to control daytime urination;

- All AEs since last visit will be recorded and assessed.

If it is not possible to perform the visit at site due to COVID-19 pandemic related constraints, at the very least a phone or video call should be placed by investigator to remotely enquire about:

- New AE occurred since last visit;
- Follow-up on previously reported AE;
- Any change in ongoing medication and treatment since last visit;
- Other new concomitant medications/treatments if the patient experienced at least one AE

The possibility to perform urine sampling at patient's home will be assessed on case by case basis by the site staff and documented.

In case of remote Visit 3, an additional on-site visit (Visit 3-bis) should be scheduled whenever possible, at the earliest possible timepoint and no later than 30 days after the IMP injection. All tasks or assessments planned for the Visit 3 at site will be performed during Visit 3-bis.

8.1.4 Safety Follow-up – Visit 4 – Day 90

During this visit, the following tasks or assessments will be performed in patients from both cohorts:

- A 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 undertaken. In case of the detection of one or more of the listed symptoms that lead to suspect NSF, a report form for SAE, AESI or pregnancy must be completed and reported.
- Any GBCA injection since the last visit will be documented;
- Other concomitant medications/treatments will be documented if related to the reported AE.
- Spot urine sample will be collected to measure concentration of the excreted gadopiclenol in patients able to control daytime urination;
- Non-serious AE related to the drug or to the trial, Serious Adverse Event (SAE) and Adverse Event of Special Interest (AESI) since the last visit will be recorded and assessed.

If it is not possible to perform the visit at site due to COVID-19 pandemic related constraints, at the very least a phone or video call should be placed by investigator to remotely enquire about:

- Non-serious AE related to the drug or to the trial, Serious Adverse Event (SAE) and Adverse Event of Special Interest (AESI) since the last visit;
- Any GBCA injection since the last visit;
- Other concomitant medications/treatments if related to the reported AE

The possibility to perform urine sampling at patient's home will be assessed on case by case basis by the site staff and documented.

In case of remote Visit 4, an additional on-site visit (Visit 4-bis) should be scheduled whenever possible, at the earliest possible timepoint and no later than 120 days after the IMP injection. All tasks or assessments planned for the Visit 4 at site will be performed during Visit 4-bis.

8.2 Imaging Characteristics

8.2.1 Equipment

MRI units with 1.5T or 3T magnetic field will be used, regardless of the manufacturer.

MRI scans will be acquired before and after gadopiclenol injection. The imaging sequences/parameters will be performed according to site's standard imaging protocol.

8.2.2 Sequences

For every patient, pre and post gadopiclenol T1-weighted SE/TSE/GRE images must be performed, and the same parameter setting must be used for unenhanced images and for gadopiclenol-enhanced images in each patient.

8.3 On Site Reading of Images

For each investigational site, a radiologist will be appointed at the start of the trial to read all images of patients included at the site.

GUERBET will document the imaging tasks and obligations of the investigational site 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 GUERBET's representative will request that investigational site submit anonymous images to GUERBET in a format agreed prior to trial start.

8.5 Other Centralized Trial Procedures

8.5.1 Pharmacokinetic procedures and assessments

Details on handling blood and urine samples for gadopiclenol assay will be provided to the site in a trial specific manual.

8.5.1.1 Blood sampling for PK (for patients from the CNS cohort)

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 (only for blood samplings performed during MRI sequences). 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. Blood samples of 1 mL each will be collected at each time point for analysis. In any case the overall trial-related blood loss will not exceed 3% of the total blood volume during a period of four weeks and will not exceed 1% for any single blood draw.

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 -20ºC (±5°C) for analysis. Plasma will be divided into two different aliquots of at least 250 µL for gadopiclenol analysis.

The labelling of the tubes will include:

- Study number
- Patient number
- Theoretical and actual time of blood collection
- Plasma

In case of remaining blood collected, it will be discarded.

The 1st aliquot for gadopiclenol determination will be sent on dry ice to the analytical centre. The second aliquot collected will be kept in the clinical centre and will be sent to the analytical centre only if necessary.

8.5.1.2 Urine sampling for PK (for patients from both cohorts)

Total urine will be collected quantitatively over 8 hours (or less if the confinement is not possible over this period due to the COVID-19 pandemic) after gadopiclenol injection in patients capable to control daytime urination to evaluate concentration of the urinary excreted gadopiclenol. The total volume of collected urine will be measured and recorded by the site.

Spot urine samples will be collected 1 week and 3 months after gadopiclenol injection to measure concentration of gadopiclenol in patients able to control daytime urination. If the urine sampling is delayed to visits V3-bis and V4-bis due to the COVID-19 pandemic the collection can take place up to 1 month and 4 months after gadopiclenol injection respectively.

After homogenization of the collected sample, urine will be divided in 2 aliquots (of maximum 5 mL each) and stored at -20°C (±5°C) until shipment to the analytical center. The 1st aliquot will be sent to the analytical center. The second aliquot collected will be kept in the clinical center and will be sent on dry ice to the analytical center only if necessary. Aliquots will be placed into polypropylene tubes, will be tightly capped and stored at -20ºC (±5°C) until shipment for analysis.

The labelling of the tubes will be as follows:

- Study number
- Patient number
- Urine
- Period of collection

After having aliquoted the samples, the remaining urine will be destroyed.

8.5.2 Central Laboratory for biological assessments

A central laboratory will be used for all scheduled laboratory tests in this trial except for the pregnancy test which will be done locally and eGFR which can be assessed locally for non-inclusion criteria verification and centrally for safety evaluation. Bedside Schwartz equation will be used for calculation of the estimated Glomerular Filtration Rate (eGFR). This formula is for use 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 in order 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 filled 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. All abnormal values considered clinically significant according to investigator's judgment will be reported as AEs and documented in the patient's source document.

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.

9. SAFETY REPORTING

The Investigator will report to the sponsor any adverse event whether related or not to the investigational medicinal product, serious or not, that occurred in a trial patient depending on the period of the trial. Special situations such as treatment errors, suspicion of transmission of an infectious agent via an IMP, unusual failure in efficacy, overdose (symptomatic or not), drug exposure during pregnancy or breastfeeding even if uneventful, suspected drug-drug interaction with another product (symptomatic or not) will also be reported to the sponsor.

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 to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A).

Any disease identified and diagnosed by trial contrast-enhanced MRI with injection of trial contrast agent will not be considered as AE. It may be collected in eCRF as medical history or trial disease.

The trial disease of the patient that met 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(s) or legal guardian (where applicable) to report any experienced abnormality as part of the usual clinical follow-up. In addition, any biological value assessed as significant by the Investigator should be considered as AE.

In order to ensure complete safety data collection, all Adverse Events occurring from the beginning of the patient's participation in the trial (Informed Consent Form signature) and until 1-week safety visit (D8), 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 according to Investigator's opinion. Non-serious AEs occurring after 1-week safety visit must be reported if related to the drug or to the trial and followed until recovery or sequelae stabilization. Serious Adverse Events (SAE) and Adverse Event of Special Interest (AESI) occurring from beginning of the patient's participation in the trial (ICF signature) and until 3-month safety visit (D90 or the day of Visit 4-bis) must be reported and followed until recovery or sequelae stabilization.

In addition, if occurring after the end of the patient's follow-up period defined for this trial, adverse events that the Investigator thinks may be associated with the trial medication/procedure must be reported to the sponsor regardless of the time between the event and the end of the trial.

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

The information relative to AE should be reported and documented in the medical file and the appropriate section of the eCRF. In case of AE remotely collected, every effort should be made to collect source documents, at least electronically, if any.

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

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 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): The real date of event end will be entered if the event has come to its end. 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 Investigational Medicinal Product:**
  - Related: the definition of adverse reaction 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 – apart from imaging procedure:**
  - Related
  - Not related
- **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.
  - 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 prior or after IMP administration, or if the Investigational Medicinal Product dosing/administration remained the same in spite of AE being present.

- 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 took a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the eCRF ("concomitant drug" 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.
  - Trial discontinuation: AE leads to a trial discontinuation

- **Assessment of the seriousness of the AE**: see Section 9.2 for SAE definition.

9.2 Serious Adverse Event

9.2.1 Definition of Serious Adverse Event (SAE)

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

- Results in death
- Is life-threatening
- Requires inpatient 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 event** that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise 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.

Note: 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 participants.

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).

9.2.2 Reporting Serious Adverse Events (SAE)

All SAEs **must be reported immediately** by the Investigator to the sponsor. Therefore, the Investigator must immediately forward to GUERBET Pharmacovigilance department a duly completed Report Form for SAE, AESI or pregnancy [redacted] provided by GUERBET with trial documents, even if it is obvious that more data will be needed in order to draw any conclusion:

- **By Fax #: + 33 (0)1 45 91 67 70**
- **Or 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.**

Information relative to SAEs, as for other reported adverse events, have to be reported also in medical file and in the appropriate section of the eCRF (Section 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 age, sex and patient's trial enrollment 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 first notification)
- Date and time of investigational drug administration,
- 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 an 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 it immediately to GUERBET Pharmacovigilance department on a Report Form for SAE, AESI or pregnancy [redacted] as a follow-up report.

The initial and follow-up reports shall identify the trial patient by his/her Identification Number assigned for the purpose of the trial.

Additional information (e.g., autopsy results, biological values …) or clarifications may be required by the Sponsor in a timely fashion to ensure accurate follow-up and assessment of each case and should be transmitted, anonymized, with a specific form [redacted] 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. The Investigator may be requested by GUERBET to provide follow-up information in order to comply with current regulations as well as for comprehensive assessment purposes.

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 the sponsor does not release the Investigator from his responsibility to inform the regulatory authorities, if applicable.

9.3 Special situations

9.3.1 Cases of overdose, lack of efficacy, drug-drug interaction, 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:

- Unintentional treatment errors (e.g., wrong route of administration),
- Misuse: where the medicinal product is intentionally and inappropriately used not in accordance with the protocol,
- Occupational exposure to an IMP,
- Overdose: administered dose above the 0.3 mmol/kg for gadopiclenol.

If one of these situations leads to an AE or SAE, the safety information will be managed as for AE or SAE accordingly and will follow the appropriate reporting procedure.

9.3.2 Pregnancy

Any participating patient who becomes pregnant or is aware of a pregnancy (patient's partner) during trial participation should inform immediately the investigational site. The female patient should be immediately withdraw from the trial and must not receive any IMP.

Any pregnancy (with or without an Adverse Event) of female adolescent participating in the trial or of partners of male adolescent participating in the trial, that is discovered after the ICF signature must be reported to GUERBET Pharmacovigilance *via* the Report Form for SAE, AESI or pregnancy [redacted] (see Section 9.2.2) unless the conception date is over one week (for GBCAs) after the last trial drug administration. In this case, there is no need to report the pregnancy to Guerbet except in case of noxious effect related to the trial drug according to investigator's opinion.

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

Specific forms "history and start of pregnancy" and "course and outcome of pregnancy" will be provided to the investigational sites. These forms will be used to collect information on the medical history of the pregnant adolescent and any risk factor of pregnancy complication, and on the follow-up and outcome of the pregnancy.

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

9.3.3 Adverse Events of Special Interest

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require 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 must be reported to GUERBET Pharmacovigilance *via* the Report Form for SAE, AESI or pregnancy [redacted] (see Section 9.2.2).

AESI for this protocol is the following: suspected or confirmed 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 safety issues that may alter the current benefit-risk assessment of an investigational medicinal product, or would be sufficient to consider changes in the trial drug administration or would involve any update of trial documents or in the overall conduct of the trial should be evaluated by the sponsor. It includes any new event likely to affect the safety of the patients 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
- 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 trial,
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,
- Recommendations of the TSRB, if any, where relevant for the safety of patients,
- Any serious adverse reaction, expected or not, involving healthy volunteers.

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 modifications
- Premature discontinuation of the trial
- Premature discontinuation of the patient

9.5 Unblinding Procedures

Not applicable.

10. PREMATURE DISCONTINUATION OF THE TRIAL

10.1 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.

10.2 Reasons for patient's premature discontinuation

Screening Failure:

A patient whose parent(s) or legal guardian (where applicable) have signed the informed consent and who discontinue the trial before gadopiclenol 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. A new patient number will be allocated to the patient.

Premature discontinuation of patients:

Patient may discontinue the trial after gadopiclenol injection for following reasons:
- Adverse Event (according to the Investigator's judgement);
- Withdrawal of patient's parent(s) or legal guardian (where applicable) consent;
- 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 medical file;
- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the trial;
- At the discretion of the Investigator if the patient safety or well-being is not compatible with trial continuation.
- Other reason (to be specified).

A reason for trial discontinuation will be documented.

Enrollment of additional patients:

Patients prematurely discontinuing the trial will not be replaced. However, if the threshold of 15 patients per age group, evaluable for the primary criterion is not reached, the enrollment will continue in order to ensure a minimum number of evaluable patients per group.
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 (SAP).

Two separate SAPs will be provided:

- a SAP for safety and efficacy
- and a SAP for population PK analysis.

Summary statistics will be presented for continuous variables, by way of n, n missing (if any), mean, standard deviation (SD), median, minimum and maximum and by way of cohort frequencies and percentages for categories of categorical variables. Percentages will be calculated using the total patients per cohort excluding missing.

Descriptive statistics for parameters of interest will be provided by age group and overall.

11.1 Statistical Method (null and alternative hypotheses)

The trial aims to evaluate the pharmacokinetic profile of gadopiclenol in plasma. So, a population PK analysis will be performed through modeling 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 for primary criterion assessment

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 PK sampling time optimization in order to determine the best possible design for the population PK modelling. The best design (in terms of sample size and sampling points) was defined as the design minimizing model's parameters root square error (RSE), hence providing the highest precision.

According to adult's data, a 2-compartment model with elimination from the central compartment described appropriately gadopiclenol pharmacokinetics. The design was evaluated for a sample size of 60 pediatric patients between 2 and 17 years old and predicted a correct estimation of all PK parameters.

As a first step, an optimization was performed on 60 children between 2 and 17 years of age. As no structural modification in the PK of children between 2 and 17 years of age was expected, a single design was optimized for a typical child of 10 years old with a body weight of 33 kg. The amount injected was calculated as following:

$n = 0{,}1 \text{ mmol/kg} \times 33 \text{ kg} = 3{,}3 \text{ mmol}$

$m = 3{,}3 \text{ mmol} \times 970.11 \text{ mg/mmol}$ (gadopiclenol molecular weight) $= 3201 \text{ mg}$

A balanced sample size within each of the age group was targeted, leading to a total sample size multiple of 3. The PK sampling time and number of patients was optimized using approaches based on the Fisher Information Matrix (FIM) for nonlinear mixed effect models, which consist in determining a balance between the number of patients and the number of samples per patient, as well as the allocation of times, according to experimental conditions [redacted]

Different designs were investigated and were compared in term of RSE and the selected design needed to provide reasonable RSE and flexibility. The predicted RSE for this design were very good and the inclusion of additional patients was not expected to impair the performance of an overall model built on all children. Thus the design with additional 20 patients aged between 0-23 months was investigated. [redacted].

A minimum of 15 patients will be included in each of the three age groups (12-17, 7-11 and 2-6 years) in order to balance the sample size between the groups. The inclusion will be completed in parallel in all groups to reach the overall number of 60 patients evaluable for the primary criterion.

11.3 Planned Analysis

11.3.1 Disposition of Patients

Number of patients and reasons for screening failure before injection will be provided per age group and overall.

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

11.3.2 Data Sets Analyzed

There will be four patient sets defined for this trial: All enrolled patients set, the Full Analysis Set (FAS), the Safety Set and the Per Protocol Set (PPS).

- All enrolled Patients Set: 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 FAS will include all patients undergoing an enhanced MRI examination in CNS and other organs. This set will be used for the Efficacy Analysis.
- Safety Set will include all patients, receiving at least one administration of study drug. This set will be used for evaluation of safety, urinary PK and gadopiclenol excretion and description of demographic data and baseline characteristics.
- The PPS will include all patients in the Safety Set undergoing an enhanced MRI examination in CNS 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

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

- No plasma PK sample was obtained
- Concomitant treatment or procedure (e.g., diuretics, clinically significant blood loss or blood transfusion) that may altered gadopiclenol pharmacokinetic parameters
- Missing information regarding time of injection and times of PK sampling (all missing)

Patients with major deviations (final list will be available prior to the analysis) will be excluded from the pharmacokinetic population analysis. All other deviations will be classified as non-major deviations. COVID-19 pandemic-related deviations will be clearly identified.

Modeling is done using all patients 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.

The actual period of quantitative urine collection will be provided and the period below 8 hours will not be considered as a deviation.

11.3.4 Demographics and Baseline Characteristics

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

- Demographic parameters: age, sex, body weight, height, race/ethnicity.
- Other baseline characteristics: childbearing potential, urinary continence, medical history, contrast media intolerance history and the prior medications / procedures defined as medications / procedures which stopped before IMP administration.

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 PK

11.3.5.1 Population PK

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,

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 age group and overall.

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

11.3.5.2 Urinary PK

Percentage of urinary excreted gadopiclenol injected dose over 8 hours and concentration of gadopiclenol excreted in spot urine samples collected at D8 (or up to D30 in case of collection at V3-bis) visit and D 90 (or up to D120 in case of collection at V4-bis) visit will be provided by age group and overall using the Safety Set.

11.3.6 Efficacy Analysis

All efficacy analyses will be done using the FAS:

- Technical adequacy for diagnosis: patient score will be tabulated qualitatively for pre and pre+post contrast images per age group, cohort and overall. Shift tables between pre and post scores will be provided.
- Assessment of contrast quality: percentage of enhancement (E%) and LBR for up to 3 most representative lesions will be tabulated quantitatively per age group, cohort and overall.
- Lesion visualization (lesion border delineation, internal morphology and contrast enhancement): for each parameter patient score will be tabulated qualitatively for pre and pre+post contrast images per age group, cohort and overall. For each MRI evaluation ("pre-contrast" and "pre+post contrast"), the number and percentage of each score of the parameter (border delineation, internal morphology, degree of contrast enhancement) will be described. A shift tables between pre and pre+post scores will be provided. The sum and variation of lesions scores and variation will be described quantitatively per age group, cohort and overall.
- Change in diagnostic confidence: following administration, the Investigators' diagnostic confidence is improved or remains unchanged or getting worse. Investigator's diagnostic confidence will be tabulated qualitatively for pre and pre+post contrast images per age group, cohort and overall.

11.3.7 Adverse Event

Adverse event analysis will be done using the Safety Set except otherwise specified.

All analyses of AEs will be based on the number of patients with AEs (and not on the number of AEs) except otherwise specified.

Events will be classified as treatment-emergent (TEAE) if they started after drug administration.

A serious AE is defined as an AE with serious classified as 'yes' or missing with each of the criteria for seriousness.

- Overall overview of Treatment Emergent AE (TEAE)

The number (%) of patients having at least one Treatment Emergent AE (TEAE) will be summarized for each age group and overall for:

- At least one TEAE
- At least one TEAE with each of the following classifications of intensity
  - Mild
  - Moderate
  - Severe
- At least one TEAE with each of the following classifications of action taken with regard to administration of the IMP:
  - No action
  - IMP interrupted

  - IMP definitively discontinued
- At least one TEAE related to trial procedure
- At least one adverse reaction (relationship to study IMP classified as 'Related')
- At least one TEAE with each of the following classifications of outcome:
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Not recovered/Not resolved
  - Fatal
- At least one TEAE leading to AE-targeted medication
- At least one TEAE leading to other AE-targeted action
- At least one serious TEAE

The table will be repeated for all Non Treatment Emergent AE (NTEAE) without presenting the adverse reaction and using the All enrolled Patients Set.

  - Distribution of AEs, AESI and SAEs

A table will be presented showing the total numbers and the distribution of AEs (number [%] of patients with 0, 1, 2 etc… AEs) for each age group and overall. The table will also show the same information for SAEs and AESI, unless the number of SAEs or AESI make this uninformative.

  - Summaries by System Organ Classes (SOC) and Preferred Term (PT)

Summaries by SOC and PT will be presented for all TEAE and all related treatment-emergent events, for each age group and overall.

11.3.8 Laboratory data

Laboratory data are defined as safety laboratory variables centrally analyzed (hematology and biochemistry) from blood samples, estimated glomerular filtration rate (eGFR) centrally calculated based on the bedside Schwartz equation and urinalysis with dipstick (see Section 7.2). 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 units and conventional 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.

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

11.3.9 Other safety observations

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

11.3.9.1 Vital signs (blood pressure, pulse rate and Blood 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 clinical significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

11.3.9.2 ECG

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

ECG data will be analyzed quantitatively and qualitatively for each age group and overall. Qualitative analyses will be done via comparison of ECG data to their normal ranges (by parameter). Quantitative analyses will be done by tabulating raw data and change from baseline.

11.3.9.3 Injection site tolerance

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

11.3.9.4 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.

11.3.9.5 Extent of exposure

Duration between IMP administrations and end of trial, volume theoretically administered (ml), volume actually administered (ml), site of administration, manual / power injector administration. If power injector administration actual rate of administration (ml/s) and theoretical rate of administration (ml/s) will be tabulated. Frequency tabulation of theoretical volume actually administered and theoretical rate of administration actually performed (yes/no) will be also displayed.

11.3.9.6 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 Statistical/Analytical issues

11.4.1 Adjustments for Covariates

Identification of covariates that are predictive of pharmacokinetic variability will be an important part of the modelling strategy.

Two sets of covariates will be considered. First, covariates know a priori to be highly influential for physiologic reasons will be considered during the structural model building in order to ensure model stability. These covariates may include for pediatric population body weight, age or eGFR for example.

In a second step, variability in PK may be identified and characterized by addition of covariates to the model. The inclusion of these covariates will follow a two steps approach. The first step will consist on an univariate screening of each covariate and the second step as a backward deletion procedure of each covariate from a full model including all covariates found significant during the first step.

Typically, both steps will be based on likelihood ratio tests, performed at the 5% level for the univariate step and at the 0.5% for the second step.

All covariates to be investigated will be pre-defined in the PK statistical analysis plan.

11.4.2 Handling of Dropouts or Missing Data

As a general rule, missing concentration data will not be imputed for the population PK modeling and values below the limit of quantification (BLQ) will be considered as missing unless they represent more than 15% of the total number of concentrations. In that case, an alternative method considering the values BLQ as censored will be considered.

Missing information regarding product administration will not be imputed and will lead to patient removal from the analysis.

In case of missing date or time for sampling, no imputation will be performed and the sample will not be considered for the analysis.

In case of missing covariate value, the population median or the most reported category (for categorical covariate) will be imputed. If more than 15% of the patients present a missing value for a covariate, it will not be considered for the analysis.

For efficacy and safety data, Missing Data will not be imputed and only observed data will be described.

11.4.3 Interim Analyses and Data Monitoring

No formal interim analysis is planned for this trial. However, after the injection of the first 15 patients included in age groups of Adolescents and Preadolescents, Trial Safety Review Board (TSRB) will be planned in order to assess safety data and to decide trial continuation.

11.4.4 Multicenter Trials

Potential differences between centers that may impact the pharmacokinetics of gadopiclenol are not expected in this trial, therefore the center will not be considered for the population PK model unless there is sufficient evidence to invalidate this assumption. In that case, the center will be considered as a covariate.

11.4.5 Multiple Comparisons/Multiplicity

Multiplicity will affect only the covariates model building in the modeling process. In order to protect the overall type I error, the backward deletion process will be performed at the 0.5% level.

11.4.6 Use of an "Efficacy Subset" of Patients

Efficacy is a secondary analysis and will be analyzed using FAS which will include all patients undergoing contrast-enhanced MRI examination in CNS and other organs.

11.4.7 Active-Control Trials Intended to Show Equivalence

Not-applicable.

11.4.8 Examination of Subgroups

No subgroup analysis will be performed in this trial. The 3 age groups specificities will be considered in the population PK model through representative structural covariates (for example weight, age, eGFR).

12. TRIAL COMMITTEES

Trial Safety Review Board (TSRB)

Trial Safety Review Board (TSRB) is set up to perform a risk/benefit assessment in order to weight possible safety disadvantages against a possible gain in efficacy 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.

TSRB is responsible for the careful review of the safety data of first 15 patients recruited in each age group from either CNS or both cohorts. Review of safety will be based on disposition demography and other baseline characteristics as well as all safety parameters (AE, laboratory data and other safety observation such as vital signs and ECG data).

The decision to start the inclusion in the group of patients aged 7-11 and 2-6 years will be taken based on safety assessment over one-day period after injection of the respective previous group. 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 patient in.

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 5 version dated 15 Decembre 2016
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A Current Step 4 version dated 27 October 1994
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials E8 Current Step 4 version dated 17 July 1997
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for 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
- EMA/141885/2020 Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic version 2 dated 27 March 2020
- EMA/158330/2020, Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials Draft dated 25 March 2020
- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards dated March 2020 Updated on April 16, 2020

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

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

In case of modifications to the trial protocol, patient parent(s) or legal guardian (where applicable) Informed Consent Form or any other written information provided to the patients or patients parent(s) or legal guardian (where applicable), or to any trial procedure; the modified documents will be submitted to IRB/IEC and Regulatory/Competent Authority opinions. Modifications may be implemented when the final approval and authorization are available.

In case of an emergency situation when the patients' safety may be at risk, 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)

Notifications 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-compliances / 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 Parent(s) or Legal Guardian (where applicable) Informed Consent

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

- Blood sampling, methodology and duration of the trial;
- Potential benefits, foreseeable risks and inconveniencies related to the trial;
- Rights and responsibilities of patients 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 child should participate in the informed consent process together with the parent(s) or legal guardian (where applicable), in a way that is appropriate to his or her age and maturity.

The language used when informing the patients and their parents 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 and their parents or legal guardian must be given ample time to decide whether they agree to participate or not.

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

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

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

13.4 Trial Records and Archiving

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 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 15 years after trial completion. Sites should obtained 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, MR images or digital supports.

- For this trial, the following will be considered as source data (as a minimum): patients medical files, MR images, ECG records.
- 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 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; 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 visits and report all discussions, patient and IMP data verification performed with particular attention to patients' safety and well-being and trial data accuracy and completeness.

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.

The Investigator or the designated person from his/her team agrees to complete the eCRF, at each patient visit, and all other documents provided by 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 and ECG can be recorded directly on the eCRF (i.e., no prior written or electronic record of data), and to be considered to be source data.

14.3.2 Data Reported in the eCRF according to Patient Status

For screening failure/non selected patients, only the date of visit, the date of informed consent signature, demographic data, eligibility criteria, the adverse event, the reason for non-selection and the date of study end will be reported.

For included patients, withdrawn before the administration of the IMP, only the selection data, the safety data, the reason for discontinuation and the date of study end will be reported.

For patients withdrawn from the trial after the administration of the IMP, 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, etc.). 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 (where applicable) withdraws consent for further data collection/participation for/in the trial.

14.3.3 Data Management System

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

Data processing and control will be closely managed by 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 of the documents relevant to the trial.

[redacted]

[redacted]

16. REFERENCES

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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 whose consent to participation was not adequately collected.

18. APPENDICES

Not applicable.