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STATISTICAL ANALYSIS PLAN 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

SPONSOR GUERBET B.P. 57400 95943 ROISSY CHARLES DE GAULLE CEDEX - FRANCE Tel.: 33-1-45-91-5000 Fax: 33-1-45-91-5199	**STATISTICAL ANALYSIS PLAN APPROVAL**
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[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino Transferase
AST	Aspartate amino Transferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
BW	Body Weight
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CNS	Central Nervous System
CSR	Clinical Study Report
CT	Computed Tomography
D	Day
DBP	Diastolic Blood Pressure
ECG	Electro Cardio Gram
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
GBCA	Gadolinium-Based Contrast Agent
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IWRS	Interactive Web Response System
LBR	Lesion to Background Ratio
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal range
MedDRA	Medical Dictionary For Regulatory Activities
MCV	Mean red blood Cells Volume
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NSF	Nephrogenic Systemic Fibrosis
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term / Prothrombin Time
RBC	Red Blood Cell
ROI	Region Of Interest
SAE	Serious Adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	Standard International
SOC	System organ Class
SpO2	Pulse Oxymetry
SS	Safety Set
TEAE	Treatment Emergent Adverse Event

TSRB	Trial Safety Review Board
ULN	Upper Limit of Normal Range
US	United States
W	Window
WBC	White Blood Cells
WHO	World Health Organization

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1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for safety and efficacy for Guerbet, 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".

This analysis plan is based on the final protocol Version 4.0 [redacted]

This document does not include the statistical analyses that meet the pharmacokinetics (PK) objectives. A specific SAP for population PK analysis will be written separately, as well as, a specific analytical PK report for concentrations data and urinary excretion.

1.1. Study objectives

The objectives of the study are defined for two cohorts of pediatric population aged from 2 to 17 years. The first one includes patients undergoing central nervous system (CNS) contrast-enhanced Magnetic Resonance Imaging (MRI): CNS cohort. The second one includes patients undergoing contrast-enhanced MRI for diseases of other organs: Body cohort.

The primary objective of the trial is to evaluate the PK 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 CNS MRI (CNS cohort).

The secondary objectives are:

- To evaluate the safety (clinical and biological) of gadopiclenol up to 3 months following single administration in both CNS and Body cohorts
- To evaluate the 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).**
- To evaluate the efficacy of gadopiclenol-enhanced MRI for CNS and Body cohorts as assessed by on-site Investigator.

1.2. Study design

GDX-44-007 is an open-label, uncontrolled, multicenter international, non-randomized, single dose design phase II trial.

The design is evaluated for a sample size of 60 patients in CNS cohort between 2 and 17 years old and predicted a correct estimation of all PK parameters. Patients are recruited into 3 predefined age groups:

- Age group 1: Adolescents 12-17,
- Age group 2: Preadolescents 7-11
- Age group 3: Young Children 2-6 years.

The total sample size of 80 patients (60 patients in CNS cohort and 20 patients in Body cohort) was estimated sufficient for the satisfactory exploration of safety and efficacy of gadopiclenol in pediatric patients with diseases of CNS and other organs.

The total sample size is balanced between 3 age groups in such a way that:

- At least 15 patients and the number as close as possible to 20 patients are included in each age group from the CNS cohort. The inclusion is 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 are included per age group. The inclusion is completed in parallel in all age groups to reach the overall number of 20 patients in the Body cohort.

The duration of the trial for a patient is about 3 months with a minimum of 82 days and maximum of 111 days (up to 134 days in case V4-bis)
. Each patient will undergo 4 visits:

- The screening visit (Visit 1): up to 14 days before inclusion
- The inclusion visit (Visit 2) and the confinement period:
    - The inclusion visit between the following days (D): D1 (gadopiclenol administration) and D2 including the confinement period (if not prevented by the constraints linked to the COVID-19 pandemic)
    - 4 sampling windows (W) covering the first 8 hours after gadopiclenol administration
        - W1: 1 to 20 min
        - W2: 30 to 45 min
        - W3: 2 to 3 hours
        - W4: 7 to 8 hours
- The 1-week safety follow-up (D8 – Visit 3) followed by V3-bis: 1-month maximum safety follow-up if V3 was done by phone or video)
- The 3-month safety follow-up (D90 – Visit 4) (followed by V4-bis: 4-month maximum safety follow-up if V4 was done by phone or video);

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

At screening visit, the following demographic data are collected:

- Age: Years and Months
- Gender: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic nor Latino
- Race (multiple choices): American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific islander, White, Other (specify)

At inclusion visit, additional demographic variables are collected:

- Age: Years and Months (if the dates of screening visit and inclusion visit are different)
- Weight (kg)
- Height (cm)

Baseline characteristics are:

- Physical examination (at screening visit)
    - Examination performed: Yes, No (and Reason in case of No)
    - If examination performed, abnormalities:
        - Yes, No
        - If yes, type of abnormalities (multiple choices): General appearance, Skin, Neck, Eyes, Ears, Nose, Throat, Lungs, Heart, Abdomen, Back, Lymph nodes, Extremities, Peripheral vascular and neurological examination, other (specify)
- Patient's medical/surgical history and concomitant diseases at screening visit
    - They will be coded using the MedDRA dictionary, version 23.0 – Apr 2020.

  - Medical histories are those "Not Ongoing" and concomitant diseases are those "Ongoing" at the screening visit.
- Urine collection data
  - Ability to control daytime urination at inclusion visit: Yes, No
  - Total urine collection over 8 hours after gadopiclenol injection: Yes, No
  - If total urine over 8 hours collected, volume of collected urine (mL)
- Childbearing potential for female patient (at inclusion visit): Yes, No
  - Pregnancy test performed (only for female patient with childbearing potential): Yes, No
  - Result of test: Negative, Positive
- Prior medications and procedures
  - Previous medications are medications ended before the gadopiclenol administration. They correspond to medications with the start period and end of treatment entered in categories: 1 = "More than 7 days before gadopiclenol administration", 2 = "Between 2 and 7 days before gadopiclenol administration, 3 = "1 day before gadopiclenol administration".
  - Patient's previous medications will be coded using the World Health Organization (WHO) Drug dictionary at least version B3 WHO DDE mars 2020
  - Patient's prior procedures related to a reported adverse event (AE) will be coded using the MedDRA dictionary version 23.0 – Apr 2020

- Previous experience with contrast agent administration (inclusion visit): Yes, No
  - Number of examinations per type of product
  - Adverse reaction during these examinations: Yes, No
  - Administration received within 7 days before the inclusion visit: Yes, No

MRI examination is described by:
- Examination performed: Yes, No
- Brand name
- MRI machine field strength: 1.5T, 3T
- Date of MRI examination
- Reader's name
- MRI examination
  - CNS Cohort: Brain / Spine
  - Body Cohort: Head and neck / Thorax / Abdomen / Pelvis / Musculoskeletal system (including extremities)
- Pre-injection and post-injection MRI sequence performed: Yes, No by MRI sequence:
  - Brain T1-weighted axial
  - Spine T1-weighted sagittal
  - Head and neck T1-weighted
  - Thorax T1-weighted
  - Abdomen T1-weighted
  - Pelvis T1-weighted
  - Musculoskeletal T1-weighted

2.2. PK data (Primary criteria and secondary criteria)

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

- Simulated concentrations at 10, 20 and 30 minutes post injection
- Area Under the Curve (AUC)

- Elimination half-life ($T_{1/2}$)
- Total clearance (C_T)
- Volume of distribution (V_d)

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 describes the gadopiclenol assays in plasma and urine samples and urinary excretion.

[redacted]

[redacted]

2.3. Safety criteria (Secondary criteria)

2.3.1. Extent of Exposure

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

The study participation durations are as follows:

- Duration between the ICF signature and the gadopiclenol injection (in days): date of gadopiclenol injection – date of ICF signature + 1
- Duration between the gadopiclenol injection and the end of the confinement period (in days): date of the day 2 visit 2– date of gadopiclenol injection + 1
- Duration between the gadopiclenol injection and the one-week follow-up date visit (in days): date of the one-week follow-up visit – date of gadopiclenol injection + 1
- Duration between the gadopiclenol injection and the three-month follow-up date visit (in days): date of the three-month follow-up visit – date of gadopiclenol injection + 1

The study contrast agent administration modalities are defined by the following parameters:

- Gadopiclenol administered (Yes/No)
- Overdose occurred (Yes/No)
- Administered treatment number
- Mode of injection (Manual/Power injector)
- Injection rate (mL/s)
- Volume of saline flush (mL)
- Volume actually administered (mL)

The patient's theoretical dose of contrast agent is calculated for each patient and is provided by the IWRS. The patient's actual dose administered is recorded in the eCRF. When the actual dose is different from the theoretical dose, the reason has to be given and recorded in the eCRF. The difference in mL and in % will be calculated:

$$\text{Difference (mL)} = \text{Volume actually administered (mL)} - \text{Theoretical calculated volume (mL)}$$

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

2.3.2. Adverse Events

Adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities (MedDRA),version 23.0 – Apr 2020.

All AEs occurring from the beginning of the patient's participation in the trial (signature of Informed Consent Form (ICF) and until 1-week safety visit (D8)), must be reported and followed even if no gadopiclenol was administered. Non-serious AEs occurring before gadopiclenol 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.

- A serious AE is defined as an event serious AE with seriousness classified as "Yes"
- An AESI for this protocol is defined by suspected or confirmed Nephrogenic Systemic Fibrosis (NSF). The MedDRA code 10067467 corresponding to the PT "Nephrogenic systemic fibrosis" will be used to identify these AESI.

Events will be classified as treatment-emergent (TEAE) if they occurred after the start time of gadopiclenol administration. If the date of the event is incomplete or missing, the event will be considered as TEAE.

2.3.3. Clinical laboratory evaluation

Safety laboratory variables centrally analyzed from blood samples are collected:

- at screening visit
- 1 day after gadopiclenol injection

The following tables list in order all parameters in both standard international units (SI) and conventional United States units (US):

Table 1 Hematology parameters

Hematology parameters	US Units	SI Units
Erythrocytes	$10^6/\mu L$	$10^{12}/L$
Hemoglobin	g/dL	g/L
Hematocrit	%	L/L
Mean red blood cell volume (MCV)	fL	fL
Leukocytes	$10^3/\mu L$	$10^9/L$
Neutrophils	$10^3/\mu L$	$10^9/L$
Neutrophils/Leukocytes	%	%
Lymphocytes	$10^3/\mu L$	$10^9/L$
Lymphocytes/Leukocytes	%	%
Monocytes	$10^3/\mu L$	$10^9/L$
Monocytes/Leukocytes	%	%
Eosinophils	$10^3/\mu L$	$10^9/L$
Eosinophils/Leukocytes	%	%
Basophils	$10^3/\mu L$	$10^9/L$
Basophils/Leukocytes	%	%
Platelet count	$10^3/\mu L$	$10^9/L$

Table 2 Biochemistry parameters

Biochemistry parameters	US Units	SI Units
Sodium	mEq/L	mmol/L
Potassium	mEq/L	mmol/L
Chloride	mEq/L	mmol/L
Calcium	mg/dL	mmol/L
Phosphorus	mg/dL	mmol/L
Glucose	mg/dL	mmol/L
Total proteins	g/dL	g/L
Creatinine	mg/dL	µmol/L
eGFR*	mL/min/1.73m²	mL/min/1.73m²
Blood Urea Nitrogen (BUN)	mg/dL	mmol/L
Aspartate amino transferase (AST)	U/L	U/L
Alanine amino transferase (ALT)	U/L	U/L
Alkaline phosphatase	U/L	U/L
Total bilirubin	mg/dL	µmol/L
Conjugated/Direct bilirubin	mg/dL	µmol/L
Lactate dehydrogenase (LDH)	U/L	U/L

*eGFR centrally calculated based on the bedside Schwartz equation

Table 3 Coagulation parameters

Coagulation parameters	US Units	SI Units
Prothrombin Time (PT) / International Normalised Ratio (INR)	NA	NA
PT	Sec	Sec

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

Vital signs include the following parameters:
- Temperature (°C)
- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Pulse Rate (bpm)
- Blood oxygen saturation (pulse oximetry) (SpO2)

ECG data include:
- Heart Rate (HR) (bpm)
- ST segments
    - Isoelectric
    - Elevation
    - Depression
- T-wave morphology
    - Normal
    - Abnormal
- U-wave morphology
    - Normal
    - Abnormal
- Global morphology
    - Normal
    - Abnormal

and the following intervals:
- RR (ms)
- PR (ms)
- QRS (ms)
- QT (ms)
- QTc Fridericia's
- QTc Bazett's

A notable QTc change is defined as a
- QT_C (Fridericia's or Bazett's) interval > 450 ms

or
- An increase of > 30 ms from baseline

Vital signs and ECG data are measured at several time points:
- Prior to gadopiclenol injection
- 30-90 min after gadopiclenol injection
- 1 day after gadopiclenol injection

Tolerance at the injection site (eruption, extravasation, inflammation and/or other) is evaluated during the gadopiclenol injection, 30-90 min after the injection and 1 day after gadopiclenol injection.

Physical examination is performed (Yes/No) at
- 1 day after gadopiclenol injection
- 1-week follow-up safety visit (D8 or up to D30 in case of V3-bis)

If yes, only new abnormalities are reported since the last visit.
Additionally, a specific physical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) is performed at 3-month follow-up visit (D 90 or up to D120 in case of V4-bis) (Yes/No) using a specific checklist of clinical symptoms potentially related to NSF.

2.3.5. Concomitant medications and procedures

Patient's concomitant medications / procedures are treatments / procedures on-going at D1 or administered until 1-week safety visit (D8). A treatment who started before the gadopiclenol administration and ongoing after gadopiclenol administration is considered as a concomitant medication.

Patient's concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary at least version B3 WHO DDE mars 2020 and tabulated by ATC code.

Patient's concomitant procedures related to a reported AE will be coded using the MedDRA dictionary version 23.0 – Apr 2020.

2.4. Efficacy criteria

Unenhanced MRI (pre) and Gadopiclenol-enhanced MRI (post) in the CNS and Body cohorts will be evaluated by on site radiologist on following parameters:

- Images adequacy
  - Technical adequacy for diagnosis using a 4-point scale
    - Non-diagnostic
    - Poor
    - Fair
    - Good
  - Assessment of images
    - Images assessable: Yes, No
    - If no, reasons
      - Artifacts due to patient
      - Artifacts due to machine
      - Injection technical failure
      - Inadequate anatomic coverage
      - Other
  - Total number of detected lesions

- Evaluation of lesions (3 most representatives lesions)
  - Location (multiples choices)
  - Largest diameter of the legion
  - Signal Intensity (SI) of the lesion
  - SI of background (SI_b) (post only)

- Assessment of contrast quality through the percentage of enhancement (E%) and the Lesion to Background Ratio (LBR) for up to 3 most representative lesions will be calculated:
  - Percentage of enhancement (E%) of lesion will be calculated by using the equation below:

$$E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} * 100\ \%\ \ with\ \begin{cases} SI_{post} = SI\ of\ lesion\ on\ post\ injection\ images \\ SI_{pre} = SI\ of\ lesion\ on\ pre\ injection\ images \end{cases}$$

  - Lesion to Background Ratio (LBR) will be calculated by using this formula:

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

$$with \begin{cases} SI_{post} = SI\ of\ lesion\ on\ post\ injection\ images \\ SI_b = SI\ of\ background\ (surrounding\ healthy\ tissue\ of\ the\ lesion)\ on\ post\ injection\ images \end{cases}$$

- Lesion visualization trough the following parameters: lesion border delineation, internal morphology and contrast enhancement. Each parameter is assessed using a 4-point scale. The Investigator will record each of lesion visualization variables for up to 3 most representative enhancing lesions.
    - Lesion border delineation 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 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 will be assessed through 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 assessed using following description:
    - Improved
    - Remains unchanged
    - Getting worse

- Following contrast-enhanced MRI, the main diagnosis is also described:
    - Primary tumor
    - Secondary tumor
    - Inflammatory disease
    - Infectious disease
    - Vascular disease
    - Congenital malformation
    - Neurodegenerative diseases
    - Other

3. STATISTICAL METHODS

This plan presents only the statistical method of safety and efficacy evaluation.

3.1. General considerations

With regards to the ICH topic E9, it has been decided that this study does not enter in the scope of the addendum. Indeed, efficacy is a secondary analysis and PK primary analysis does not aim to show treatment effect.

After the database lock, the statistical analysis will be performed by the CRO [redacted] under the supervision of the Guerbet Biostatistician, based on the present document.

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

Thorough description of all parameters reported will be presented separately by age group (CNS and Body cohorts confounded), overall in the CNS cohort, overall in the Body cohort, and overall (CNS and Body cohorts confounded) unless otherwise specified (particularly for efficacy data). Summary tabulated results will be provided by assessment time, if relevant, or they will be replaced by the corresponding individual data listings if too few patients are concerned.

Baseline definition

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

Unscheduled measures after the gadopiclenol administration will not be taken into account in the descriptive statistical analysis. These will only be listed.

Quantitative parameters

Summary statistics (Number [n], Mean, Standard Deviation (SD), Median, Minimum, Maximum and Missing) will be calculated for quantitative variables. If for a given parameter, the raw value has been collected with x decimal places, the mean, median and SD will be rounded to x+1 decimal places, while the minimum and maximum values will be tabulated as reported with x decimal places.

Qualitative parameters

Number of patients and percentages will be presented for categorical variables. Percentages will be rounded to one decimal place. The denominator will be the number of patients (excluding missing) in the set presented.

For laboratory data, the comparison of parameter values to their normal ranges will be done based on the following categories:

- < LLN (Lower Limit of Normal range)
- > ULN (Upper Limit of Normal range)

Software

SAS® Version 9.4 will be used for all descriptive summaries and statistical analyses.

3.2. Null and alternative hypothesis

No inference will be drawn from this trial which is only descriptive. Therefore, neither null nor alternative hypotheses will be carried out.

3.3. Determination of 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.

A sample size of 60 pediatric patients between 2 and 17 years old was determined to be adequate for this design and to predict a correct estimation of all PK parameters. The total sample size of 80 patients was estimated enough for the satisfactory exploration of safety and efficacy of gadopiclenol in pediatric patients with diseases of CNS and other organs.

The decision to start the next age group is 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 is completed in parallel with the start of the next group.

3.4. Adjustment for covariates

The statistical analysis for the safety and efficacy evaluation of the gadopiclenol is only descriptive. No adjustment is necessary. (Not applicable)

3.5. Handling of dropouts or missing data

No imputation will be performed in this trial for efficacy and safety data.

3.6. Interim analyses and data monitoring

No interim analysis is planned for this trial.

However, TSRB is planned after injection of the first 15 patients recruited in each age group (leading to 4 TSRB) to assess safety data and to decide the trial continuation. One final TSRB is planned at the end of recruitment to assess safety. Review of safety is 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).

3.7. Multicenter studies

No formal analyses by center will be performed; however, the number of exposed patients will be described by center.

3.8. Multiple comparisons/Multiplicity

Not applicable.

3.9. Use of an “efficacy subset” of patients

Efficacy is a secondary analysis and will be analyzed using the Full Analysis Set (FAS).

3.10. Active control studies intended to show equivalence

Not applicable.

3.11. Examinations of subgroups

Not applicable

[redacted]

5. STATISTICAL AND ANALYTICAL PLANS

This SAP concerns only the evaluation of safety up to 3-months following single administration and efficacy of gadopiclenol-enhanced MRI for CNS and Body cohorts. The statistical analysis of PK data (including excretion of gadopiclenol) is not be presented in this document.

5.1. Disposition of patients

Number (%) of patients screened, receiving gadopiclenol injection, completed the study and prematurely discontinued will be presented by age group and overall, in each cohort and globally.
The following descriptions (number and percentage of patients) will be performed per age group (CNS and Body confounded), cohort and overall with regards to the disposition of patients:

- Patients present at each study visit
- Patients by center
- Patients and reasons for screening failure before injection
  - A patient who signed the ICF and discontinue at screening visit or at inclusion visit before gadopiclenol injection will be considered screening failure
- Injected patients and reasons for prematurely discontinuation
  - A patient who received the gadopiclenol injection and discontinue before the end of the study will be considered discontinued

Reasons for screening failure or for premature discontinuation will be presented separately if they are due to the COVID-19 pandemic.

If a patient withdrew for Adverse Event and at least one adverse event is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at COVID-19 but if no AE is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at Adverse Event other than COVID-19

If a patient withdrew for other reason and it is written in the specify field : “COVID-19 crisis preventing patient to follow protocol schedule” then the reason of premature withdrawal will be put at COVID-19 pandemic preventing patient from following protocol schedule but if the specify field is filled with other texts then the reason of premature withdrawal will be put at Other reason

5.2. Data Sets Analyzed and protocol deviations

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

All enrolled patients set will include all patients whose parent(s)/legal guardian have signed the ICF. This set will be used for patient disposition summaries and individual listings including AEs.

The SS will include all patients receiving at least one administration of study drug. This set will be used for evaluation of safety, description of demographic data and baseline characteristics.

The FAS will include all patients undergoing an enhanced (i.e., after gadopiclenol administration) MRI examination in CNS and other organs. This set will be used for the efficacy analysis.

The PPS will include all patients in the SS undergoing an enhanced MRI examination in the CNS cohort only without major deviations likely to impact the population PK model. This set will be used for description of demographic data and baseline characteristics.

The following table describes how the above defined patients sets will be used in the different analyses conducted.

Analyses Sets	All enrolled patients Set	Safety Set	FAS	PPS
Disposition of patients	✓			
Individual listings	✓			
Description of demographic data		✓		✓*
Baseline characteristics		✓		✓*
Efficacy assessment			✓	
Safety assessment	✓**	✓		

* If the PPS is different from the SS
** Only for overall summary of all AEs

Protocol deviations

As per International Conference on Harmonization (ICH) E3 guideline, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, with or without impact to the patient safety or the efficacy assessments. Protocol deviations are displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. The list of protocol deviations is presented in the table below and can be updated if necessary. Protocol deviations will be gathered from monitoring files, clinical database, external vendors of off-site data (Laboratory data and PK data) and PK experts [redacted]

Protocol deviations will be split in major and non-major deviations. A major deviation is defined as a deviation having an impact on the primary criteria. A first categorization is done in this document. It will be refined during the statistical data review meeting that will be held before database lock. The decisions will be duly described in the meeting minutes.

All deviations will be reviewed during the statistical data review meeting and if the cause of the deviation is related to the COVID-19 pandemic then the deviation will be presented apart with the addition of "due to COVID-19" in the corresponding description.

The deviations are listed in the table below:

Category	Description	Source	Status
Inclusion Criteria not met and patient included			
	Female or Male pediatric patient not aged from 2 to 17 years	Clinical data base	Non major
	Patient with known or suspected lesion(s) scheduled to undergo routine contrast-enhanced MRI of CNS or of other organs	Clinical data base	Non major
	Patient whose parent(s) or legal guardian (where applicable) did not provide 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	Monitoring/ Clinical data base	Major

	Patient with capacity of understanding who did not receive age- and maturity-appropriate information and did not provide his/her assent to participate in the trial (as required by national regulations)	Monitoring / Clinical data base	Major
	Patient not affiliated to national health insurance according to local regulatory requirements	Clinical data base	Non major
Non-inclusion criteria met and patient included			
	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	Clinical data base	Major
	Patient whose treatment or procedure (e.g., diuretics, clinically significant blood loss or blood transfusion) preceding or subsequent to gadopiclenol administration would alter gadopiclenol pharmacokinetic parameters	Clinical data base	Major
	Patient with acute or chronic renal insufficiency defined as estimated Glomerular Filtration Rate (eGFR) out of age-adjusted normal values [eGFR must be calculated based on bedside Schwartz equation]	Clinical data base	Non major
	Patients referred for MR angiography	Clinical data base	Non major
	Patient with history of bleeding disorder	Clinical data base	Non major
	Patient with known severe liver disease	Clinical data base	Non major
	Patient with known cardiac disease (e.g., heart rhythm anomalies, long QT syndrome)	Clinical data base	Non major
	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	Clinical data base	Non major
	Patient with electrolyte or fluid imbalance that at Investigator’s judgment presents undue risk assessed within 1 month prior to gadopiclenol administration	Clinical data base	Non major
	Patient undergoing a change in chemotherapy within 1 day prior to or 1 day after gadopiclenol administration	Clinical data base	Non major
	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	Monitoring/Clinical data base	Major
	Patient with contraindication for MRI such as iron metal implants (e.g., aneurysm clips, pacemaker)	Clinical data base	Non major
	Patient with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents	Clinical data base	Non major
	Patient with history of hypersensitivity caused by any contrast media / agents (iodine or gadolinium)	Clinical data base	Non major
	Patient with known contraindication(s) to the use of any gadolinium-based contrast agent (GBCA)	Clinical data base	Non major
	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	Clinical data base	Non major

	and must be using medically approved contraception* if sexually active]		
	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	Clinical data base	Non major
	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	Clinical data base	Non major
	Patient having participated in a clinical trial and having received any investigational product within 7 days prior to gadopiclenol administration or planned during the trial	Clinical data base	Non major
	Patient previously included in this trial	Clinical data base	Non major
	Patient related to the Investigator or any other trial staff or relative directly involved in the trial conduct	Clinical data base	Non major
Patient not withdrawn as per protocol			
	Patient becoming pregnant or discovering her pregnancy during trial participation (urine pregnancy test positive) and not withdrawn	Monitoring/Clinical data base	Non major
	Patient with calculated eGFR missing or out of age-adjusted normal values and not withdrawn	Clinical data base	Non major
Missing data			
	PK blood sample not performed, or results are missing	Clinical data base/ PK database	Non major
	No plasma PK sample was obtained	Clinical data base/ PK database	Major
	PK urine sample not performed, or results are missing	Clinical data base/PK database	Non major
	PK total urine collection not performed, or results are missing	Clinical data base/PK database	Non major
	Vital signs not measured, or results are missing	Clinical data base	Non major
	Standard 12-lead ECG not performed or results missing	Clinical data base	Non major
	Biochemistry sample not performed, or results are missing	Clinical data base/Laboratory database	Non major
	Hematology sample not performed, or results are missing	Clinical data base/Laboratory database	Non major
	Tolerance at injection site is not filled in for patient receiving gadopiclenol	Clinical data base	Non major
	Ability to control daytime urination is missing	Clinical data base	Non major
	Age is missing	Clinical data base	Non major
	Sex is missing	Clinical data base	Non major
	Weight is missing	Clinical data base	Non major

	Height is missing	Clinical data base	Non major
	Ethnicity is missing	Clinical data base	Non major
	Race is missing	Clinical data base	Non major
	Physical examination not performed	Clinical data base	Non major
	Physical examination for NSF not performed	Clinical data base	Non major
	Time of injection is missing	Clinical data base	Major
	Time of all PK sampling are missing	Clinical data base	Major
	Urine pregnancy test not performed	Clinical data base	Non major
	MRI examination not performed	Clinical data base	Non major
	MRI Machine brand name is missing	Clinical data base	Non major
	MRI machine field strength is missing	Clinical data base	Non major
	Adequate MRI sequence not performed	Clinical data base	Non major
	Follow-up one-week visit not performed	Clinical data base	Non major
	Follow-up one-week visit not performed due to COVID	Clinical data base	Non major
	Follow-up 3-month visit not performed	Clinical data base	Non major
	Follow-up 3-month visit not performed due to COVID	Clinical data base	Non major
Gadopiclenol Administration			
	The volume of gadopiclenol actually administered is different from the theoretical one by ≤20 %	Clinical data base	Non major
	The volume of gadopiclenol actually administered is different from the theoretical one by more than 20 %	Clinical data base	Major
	Actual gadopiclenol injection rate not adequate	Clinical data base	Non major
	Extravasation	Clinical data base	Major
	Gadopiclenol storage conditions not respected	Monitoring	Non major
	Patient not administered with gadopiclenol	Clinical data base	Major
Non respect of study's schedule and procedures			
	PK blood sample storage conditions not respected	Monitoring	Non major
	PK blood sample assessed out of stability period	Monitoring	Major
	Urine sample storage conditions no respected	Monitoring	Non major
	Urine sample assessed out of stability period	Monitoring	Non major
	Blood samples for PK collected out of the scheduled time windows	Clinical data base	Non major
	Blood samples for PK collected with no sufficient bio-analytical assessments to calculate reliable estimates of the PK parameters	PK expert	Major
	Urine samples for PK collected out of the scheduled time windows	Clinical data base	Non major
	Total urine collection more than 8 hours	Clinical data base	Non major

	Urine samples for PK collection date different from the day of visit	Clinical data base	Non major
	Urine samples for PK collected with no sufficient bio-analytical assessments to calculate reliable estimates of the PK parameters	PK expert	Non major
	Vital signs performed out of the scheduled time windows	Clinical data base	Non major
	Blood pressure and pulse rate not performed in supine position after a rest for at least 5 minutes	Monitoring	Non major
	Blood pressure measured on the arm used for the injection	Monitoring	Non major
	Standard 12-lead ECG not performed in supine position after a rest for at least 5 minutes	Monitoring	Non major
	ECG measured out of the scheduled time windows	Clinical data base	Non major
	Blood samples for safety storage conditions not respected	Monitoring	Non major
	Blood samples for safety collected out of scheduled time windows	Clinical data base	Non major
	Time between screening visit and gadopiclenol administration is greater than 14 days	Clinical data base	Non major
	One week safety follow-up performed out of the scheduled time windows	Clinical data base	Non major
	3 month safety follow-up performed out of the scheduled time windows	Clinical data base	Non major
	End of Study visit not performed at visit 4	Clinical data base	Non major
	IWRS recording not appropriate	Monitoring	Non major
	PK profile unexpected	PK expert	Non major
Forbidden concomitant medication			
	Patient having concomitant procedure that may altered gadopiclenol PK parameters	Monitoring/ PK expert	Major
	Patient having received concomitant treatment that may altered gadopiclenol PK parameters	Monitoring/ PK expert	Major
	Patient having received contrast agent one week before or after the gadopiclenol administration	Clinical data base	Non major
Good Clinical Practice (GCP) deviation			
	ICF management not appropriate	Monitoring	Non major

	Source document management not appropriate	Monitoring	Non major
	SAE management not appropriate	Monitoring	Non major

Frequency and percentages of patients with protocol deviations will be presented breaking down by status (major/non major).

A listing of all protocol deviations will also be provided in CSR appendix 16.2.3.

5.3. Measurements of compliance with gadopiclenol

Volume theoretically administered, volume actually administered, and difference between theoretical and actual volumes will be described by descriptive statistics using the SS per age group, cohort, and overall. The difference in mL and in % will be presented for the patients with a difference between the 2 volumes. The reasons of the differences will be only listed.

5.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be presented on the Safety Set (and possibly the PPS).

5.4.1. Demographic data

Demographic parameters and baseline characteristics will be described per age group, cohort and overall with descriptive statistics.

5.4.2. Study disease

Not applicable

5.4.3. Risk factors

Not applicable

5.4.4. Medical history and concomitant diseases

Summary tables (number and % of patients) will be presented first for medical history then for concomitant diseases per age group, cohort and overall, and tabulated by System Organ Class (SOC), Preferred Term (PT) and concomitant status. Tables will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT according overall group.

5.4.5. Prior medications and procedures

The number and percentage of patients who took concomitant medications ended before the gadopiclenol administration will be summarized according to Anatomical Therapeutic Chemical (ATC) system main group (ATC1, ATC first level corresponds to the first letter of the ATC code) for each age group, cohort and overall.

The table will be sorted according to the percentage of patients reporting at least one previous medication from the most to the least frequent globally.

Patient's prior procedures will be tabulated by SOC and PT, and sorted by decreasing frequency of SOC, and decreasing frequency of PT within SOC according overall group.

5.5. PK Evaluation

All PK analyses (population PK analysis and analytical PK analysis) are detailed in dedicated reports and will be presented on the PPS.

5.6. Safety Evaluation

All safety parameters will be presented using the SS per age group (CNS and Body mixed), cohort and overall, unless otherwise specified.

5.6.1. Extent of Exposure

All durations will be described as quantitative variables.

The modalities of the contrast agent administration will be presented as qualitative or quantitative variables. The following parameters will only be listed: administered treatment number and reason why the volume administered is different from the theoretical calculated volume.

5.6.2. Adverse Events

An overall summary of AEs in term of number of patients and number of AEs will be presented overall using the All Enrolled patients Set:

- At least one AE
- Distribution of AEs per patient (only the number and the percentage of patients with 1, 2, etc. … AEs)
- At least one AE with each of the following classification of intensity
    - Mild
    - Moderate
    - Severe
- At least one AE with each of the following classifications of outcome:
    - Recovered/resolved
    - Recovered/resolved with sequelae
    - Not recovered/Not resolved
    - Fatal
- At least one AE leading to AE-targeted medication
- At least one AE leading to other AE-targeted action
- At least one serious AE
- At least one Adverse Event of Special Interest (AESI)

An overall summary of AEs before gadopiclenol administration will be also presented using the SS.

TEAE will be presented using the SS and by age group, cohort and overall as follows:

- At least one TEAE
- Distribution of TEAEs per patient (only the number and the percentage of patients with 1, 2, etc. … TEAEs)
- At least one TEAE with each of the following classification of intensity
    - Mild
    - Moderate
    - Severe
- At least one TEAE with causal relationship to gadopiclenol
- At least one TEAE with causal relationship to the trial procedure
- 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 with each of the following classification of action taken with regard to gadopiclenol administration
    - No action
    - Gadopiclenol withdrawn
- At least one TEAE leading to TEAE-targeted medication
- At least one TEAE leading to other TEAE-targeted action
- At least one serious TEAE
- At least one AESI during the one-week safety follow-up period, and during the 3-month safety follow-up period

Summaries by SOC and PT will be presented for all TEAEs and all related TEAEs (related to IMP and related to study procedure respectively separately) using the SS. These analyses will be based on the number of patients with at least one TEAEs and the number of TEAEs.

5.6.3. Deaths, serious adverse events and other significant adverse events

All deaths, all other serious adverse events (SAE) and AESI occurred on SS will be listed per patient number, age group, cohort, with indication of date/time of onset, date of event end, Primary SOC, PT, description (investigator's wording), duration, outcome (recovered / resolved, recovered / resolved with sequelae, not recovered / not resolved, fatal), intensity (mild, moderate, severe), seriousness criteria, causal relationship to gadopiclenol (related, not related), causal relationship to a study procedure (related / not related), the action taken with regard to gadopiclenol administration (No action, gadopiclenol withdrawn), other action taken (Yes, No) and the study phase defined according to the start date of the event and the study visit: screening visit, inclusion visit before injection, inclusion visit after injection, 1-week safety follow-up, 3-months safety follow-up.

5.6.4. Clinical laboratory evaluation

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

Quantitative analyses will be done by tabulating raw data and change from baseline.

Qualitative analyses will be done via:

- Comparison of laboratory data to their reference ranges

- Shift tables presenting relative change from baseline in eGFR, creatinine and blood urea nitrogen in classes (≤ -50%, > -50% and ≤ -25%, > -25% and ≤ -15%, > -15% and < 0%, ≥ 0% and < 15%, ≥ 15% and < -25%, ≥ 25% and < 50% and ≥ 50 %) will be displayed.

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

5.6.5.1 Vital signs

Vital signs parameters will be presented at each time point as quantitative variables and qualitative variables.

Quantitative analyses will be done by tabulating raw data and changes in vital signs parameter from baseline.

Qualitative analyses will be provided according to the following classes:

- <90, [90; 160], >160 mmHg for SBP
- <10, [10; 120], >120 mmHg for DBP
- <10, [10; 200], >200 bpm for pulse rate

5.6.5.2 ECG

ECG parameters will be presented at each time point as quantitative variables and qualitative variables

If applicable, quantitative analyses will be done by tabulating raw data and changes in ECG parameter from baseline, else qualitative analyses will be presented. For QTc change, both quantitative and qualitative (>450 ms and increase > 30 ms from baseline) analyses will be provided.

5.6.5.3 Injection Site Tolerance

The number of patients experiencing eruption, extravasation, inflammation or other will be tabulated at each time point. Other events will be listed.

5.6.5.4 Physical examination

Physical examination data will be presented at each time point.

5.6.6. Concomitant medications and procedures

The number and percentage of patients who took concomitant medications started before and after gadopiclenol injection will be presented according to ATC code.

The table will be sorted according to the percentage of patients reporting at least one medication from the most to the least frequent globally.

Patient's concomitant procedures will be tabulated by body system, and PT and sorted by decreasing frequency of the SOC, and decreasing frequency of the PT within the SOC of overall group.

5.7. Efficacy Evaluation

All efficacy analyses will be done using the FAS per CNS age group, cohort and overall. When relevant, the denominator will be the number of lesion (instead of number of patients).

Gadopiclenol-enhanced MRI efficacy evaluation will be evaluated by on-site radiologist based on following parameters:

- Images adequacy (pre and post)
    - Technical adequacy for diagnosis
        - Patient score will be tabulated qualitatively for pre and post contrast images
        - Shift tables between pre and post scores will be provided.
    - Characteristics of assessment of images (assessability and reasons for non-assessability) will be tabulated qualitatively for pre and post contrast images.
    - Total number of detected lesions per subject will be presented quantitatively and qualitatively for pre and post contrast images.

- Evaluation of lesions (3 most representatives lesions) will be tabulated qualitatively (location of lesion) and quantitatively for pre (largest diameter, SI) and post (largest diameter, SI, SI_b) contrast images.

- Assessment of contrast quality will be tabulated for all parameters (E% and LBR) quantitatively.

- Lesion visualization
    - For each parameter (lesion border delineation, internal morphology and contrast enhancement), lesion score will be tabulated qualitatively for pre and post contrast images
    - A shift table between pre and post scores will be provided.
    - The sum of lesion score (patient score) and its variation (post minus pre) will be described quantitatively.

- Change in diagnostic confidence and main diagnosis will be tabulated qualitatively for post contrast images

6. LIST OF TABLES, FIGURES AND LISTINGS

6.1. Contents of clinical study report section 14

This section lists all Tables and Figures in the order in which they are expected to appear in Section 14 of the CSR.

6.1.1. Demographic data

6.1.1.1 Disposition of Patients

Table 14.1.1.1 Patient Overall Disposition – All Enrolled Patients Set – CNS Cohort
Table 14.1.1.2 Patient Overall Disposition – All Enrolled Patients Set – Body Cohort
Table 14.1.1.3 Patient Overall Disposition – All Enrolled Patients Set
Table 14.1.1.4 Disposition by Visit – All Enrolled Patients Set
Table 14.1.1.5 Number of Patients by Center – All Enrolled Patients Set
Table 14.1.1.6 Reasons for Screening Failure– All Enrolled Patients Set
Table 14.1.1.7 Reasons for Premature Discontinuation – Safety Set

6.1.1.2 Protocol Deviations

Table 14.1.2.1 Major Protocol Deviations – All Enrolled Patients Set
Table 14.1.2.2 Non Major Protocol Deviations – All Enrolled Patients Set

6.1.1.3 Data Sets Analysed

Table 14.1.3.1 Number of Patients in Safety Set – Safety Set
Table 14.1.3.2 Number of Patients in Full Analysis Set And Per Protocol Set – Safety Set

6.1.1.4 Demographics and Baseline Characteristics

Demographics characteristics

Table 14.1.4.1 Demographic Characteristics – Safety Set

If PPS are presented, the number of tables will be incremented by one.

Baseline characteristics

Table 14.1.4.2 Physical Examination at Screening Visit – Safety Set
Table 14.1.4.3 Medical/Surgical History at Screening Visit - Safety Set
Table 14.1.4.4 Urine Collection Data - Safety Set
Table 14.1.4.5 Pregnancy Test at Inclusion Visit - Safety Set
Table 14.1.4.6 Prior Medications According to ATC System Main Group - Safety Set
Table 14.1.4.7 Prior Procedures - Safety Set
Table 14.1.4.8 Previous Experience With Contrast Agent Administration - Safety Set

Table 14.1.5.1 MRI Examination – Full Analysis Set – CNS Cohort
Table 14.1.5.2 MRI Examination – Full Analysis Set – Body Cohort

If PPS are presented, the number of tables will be incremented by one.

6.1.1.5 Compliance with gadopiclenol administration

Table 14.1.5.3 Compliance With Gadopiclenol Administration – Safety Set

6.1.2. PK data

Not detailed in this SAP

6.1.3. Safety data

6.1.3.1 Extent of exposure

Table 14.3.1.1 Summary of Durations in the Study – Safety Set
Table 14.3.1.2 Study Contrast Agent Administration Modalities – Safety Set

6.1.3.2 Adverse events

Table 14.3.2.1 Adverse Events – Overall Overview – All Patients Set
Table 14.3.2.2 Adverse Events Before Gadopiclenol Administration – Overall Overview – Safety Set

Table 14.3.2.3 Treatment Emergent Adverse Events – Overall Overview – Safety Set
Table 14.3.2.4 Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Set
Table 14.3.2.5 Treatment Emergent Adverse Events With Causal Relationship to Gadopiclenol by Primary System Organ Class and Preferred Term – Safety Set
Table 14.3.2.6 Treatment Emergent Adverse Events With Causal Relationship to a Study Procedure by Primary System Organ Class and Preferred Term – Safety Set

6.1.3.3 Deaths, serious adverse events and other significant adverse events

Table 14.3.2.7 Listing of Death – Safety Set
Table 14.3.2.8 Listing of Serious Adverse Events – Safety Set
Table 14.3.2.9 Listing of Adverse Events of Special Interest – Safety Set

6.1.3.4 Laboratory data

Table 14.3.3.1 Hematology Data – SI Units – Safety Set
Table 14.3.3.2 Biochemistry Data – SI Units – Safety Set
Table 14.3.3.3 Coagulation Data – SI Units – Safety Set
Table 14.3.3.4 Hematology Data – Conventional US Units – Safety Set
Table 14.3.3.5 Biochemistry Data - Conventional US Units – Safety Set
Table 14.3.3.6 Coagulation Data - Conventional US Units – Safety Set

Table 14.3.3.7 Shift Table of Serum Creatinine, eGFR, and BUN - SI Units – Safety Set
Table 14.3.3.8 Shift Table of Serum Creatinine, eGFR, and BUN – Conventional US Units – Safety Set

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

6.1.3.5.1 Vital signs

Table 14.3.4.1 Vital Signs Data – Safety Set

6.1.3.5.2 ECG

Table 14.3.4.2 ECG Data – Safety Set

6.1.3.5.3 Other observations

Table 14.3.4.3 Physical Examination – Safety Set
Table 14.3.4.4 Injection Site Tolerance – Safety Set

6.1.3.6 Concomitant medications / Procedures

Table 14.3.4.5 Concomitant Medications Started Before Gadopiclenol Administration According to ATC Drug Dictionary – Safety Set
Table 14.3.4.6 Concomitant Medications Started After Gadopiclenol Administration According to ATC Drug Dictionary – Safety Set
Table 14.3.4.7 Concomitant Procedures – Safety Set

6.1.4. Efficacy data

Table 14.2.1 Images Adequacy And Number of Lesions Detected – Unenhanced MRI – Full Analysis Set
Table 14.2.2 Images Adequacy And Number of Lesions Detected – Contrast-Enhanced MRI – Full Analysis Set
Table 14.2.3 Technical Adequacy For Diagnosis Between Unenhanced And Contrast-Enhanced MRI – Full Analysis Set

Table 14.2.4 Evaluation of Lesions – Unenhanced MRI – Full Analysis Set
Table 14.2.5 Evaluation of Lesions – Contrast-Enhanced MRI – Full Analysis Set

Table 14.2.6 Assessment of Contrast Quality – Full Analysis Set

Table 14.2.7 Lesion visualization – Unenhanced MRI – Full Analysis Set
Table 14.2.8 Lesion visualization – Contrast-Enhanced MRI – Full Analysis Set
Table 14.2.9 Lesion Border Delineation Between Unenhanced And Contrast-Enhanced MRI – Full Analysis Set
Table 14.2.10 Internal Morphology Between Unenhanced And Contrast-Enhanced MRI – Full Analysis Set
Table 14.2.11 Degree of Contrast Enhancement Between Unenhanced And Contrast-Enhanced MRI – Full Analysis Set
Table 14.2.12 Sum of Lesions Scores and Variation – Age Group 1 in CNS Cohort– Full Analysis Set
Table 14.2.13 Sum of Lesions Scores and Variation – Age Group 2 in CNS Cohort – Full Analysis Set
Table 14.2.14 Sum of Lesions Scores and Variation – Age Group 3 in CNS Cohort – Full Analysis Set
Table 14.2.15 Sum of Lesions Scores and Variation – CNS Cohort – Full Analysis Set
Table 14.2.16 Sum of Lesions Scores and Variation – Body Cohort – Full Analysis Set
Table 14.2.17 Sum of Lesions Scores and Variation – All Cohorts – Full Analysis Set
Table 14.2.18 Change in Diagnosis Confidence – Full Analysis Set

6.2. Contents of clinical study report section 16.2

This section lists all Listings in the order in which they are expected to appear in the CSR.

6.2.1. Demographic Data

6.2.1.1 Disposition of Patients

Listing 16.2.1.1 Patient Disposition – All Enrolled Patients Set
Listing 16.2.1.2 Patient Status – All Enrolled Patients Set
Listing 16.2.1.3 Inclusion Criteria Not Met – All Enrolled Patients Set
Listing 16.2.1.4 Non-Inclusion Criteria Met – All Enrolled Patients Set

6.2.1.2 Protocol Deviations

Listing 16.2.1.5 Major Protocol Deviations – All Enrolled Patients Set
Listing 16.2.1.6 Non Major Protocol Deviations – All Enrolled Patients Set

6.2.1.3 Data Sets Analysed

Listing 16.2.1.7 Analysis Data Sets – All Enrolled Patients Set

6.2.1.4 Demographics and Baseline Characteristics

Listing 16.2.1.8 Demographics – All Enrolled Patients Set
Listing 16.2.1.9 Physical Examination – All Enrolled Patients Set
Listing 16.2.1.10 Medical/Surgical History – All Enrolled Patients Set
Listing 16.2.1.11 Total Urine Collection – All Enrolled Patients Set
Listing 16.2.1.12 Urine Pregnancy Test– All Enrolled Patients Set
Listing 16.2.1.13 Concomitant Medications – All Enrolled Patients Set
Listing 16.2.1.14 Prior Procedures – All Enrolled Patients Set
Listing 16.2.1.15 Previous Experience With Contrast Agent Administration – All Enrolled Patients Set

6.2.2. PK Data

Not applicable

6.2.3. Safety Data

6.2.3.1 Extent of exposure

Listing 16.2.3.1 Summary of Durations in the study – All Enrolled Patients Set
Listing 16.2.3.2 Study Contrast Agent Administration Modalities – All Enrolled Patients Set

6.2.3.2 Adverse Events

Listing 16.2.3.3 Adverse Events – All Enrolled Patients Set

6.2.3.3 Death

All listings are including with tables in the last section.

6.2.3.4 Laboratory Data

Listing 16.2.3.4 Hematology Data – SI Units – All Enrolled Patients Set
Listing 16.2.3.5 Biochemistry Data – SI Units – All Enrolled Patients Set
Listing 16.2.3.6 Coagulation Data – SI Units – All Enrolled Patients Set
Listing 16.2.3.7 Hematology Data – Conventional US Units – All Enrolled Patients Set
Listing 16.2.3.8 Biochemistry Data – Conventional US Units – All Enrolled Patients Set
Listing 16.2.3.9 Coagulation Data – Conventional US Units – All Enrolled Patients Set

6.2.3.5 Vital Signs, physical findings and other observations

Listing 16.2.3.8 Vital Signs – All Enrolled Patients Set
Listing 16.2.3.9 ECG Parameters – All Enrolled Patients Set
Listing 16.2.3.10 Injection Site Tolerance – All Enrolled Patients Set

6.2.4. Efficacy Data

Listing 16.2.4.1 MRI Examination – All Enrolled Patients Set
Listing 16.2.4.2 MRI Sequence – All Enrolled Patients Set
Listing 16.2.4.3 MRI Evaluation – All Enrolled Patients Set
Listing 16.2.4.4 Lesions Evaluation – Unenhanced MRI – All Enrolled Patients Set
Listing 16.2.4.5 Lesions Evaluation – Contrast-Enhanced MRI – All Enrolled Patients Set
Listing 16.2.4.6 Contrast Quality – All Enrolled Patients Set

[redacted]