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STATISTICAL ANALYSIS PLAN No GDX-44-004

P03277 DOSE FINDING STUDY IN CENTRAL NERVOUS SYSTEM (CNS) MAGNETIC RESONANCE IMAGING (MRI)

Phase IIb clinical study

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HISTORY FORM

Version	Date	Reason for change
1.0	09 JAN 2018	Initial version.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALT	Alanine Amino Transferase
ANOVA	ANalysis Of VAriance
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
bpm	beats per minute
BUN	Blood Urea Nitrogen
BW	Body Weight
CI	Confidence Interval
CNR	Contrast to Noise Ratio
CNS	Central Nervous System
CSF	CerebroSpinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CZ	Czech Republic
DBP	Diastolic Blood Pressure
ECG	ElectroCardioGram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
ICC	Intra-Class Correlation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ITT	Intention To Treat
IWRS	Interactive Web Response System
LBR	Lesion-to-Brain Ratio
LDH	Lactate DeHydrogenase
LLT	Lowest Level Term
LS	Least Squares
MAR	Missing At Random
MCV	Mean Corpuscular Volume
MED	Minimum Effective Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PPS	Per Protocol Set
PT	Preferred Term
Q-Q	Quantile-Quantile
RBC	Red Blood Cells
ROI	Region Of Interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

SD	Standard Deviation
SI	Signal Intensity *or* Standard International
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogic Scale
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 Guerbet, Protocol No. GDX-44-004: "P03277 Dose Finding Study in Central Nervous System (CNS) Magnetic Resonance Imaging (MRI)".

This analysis plan is based on the protocol Version 2.0 including amendment n°1 dated 11 July 2016.

1.1. Study objectives

The primary objective is to determine a safe and effective dose of P03277 based on a comparison of Contrast to Noise Ratio (CNR) between several doses, 0.025, 0.05, 0.1 and 0.2 mmol/kg of P03277 and MultiHance® at 0.1 mmol/kg.

The secondary objectives of the trial are:

- To assess technical adequacy of images.
- To evaluate capacity of lesion detection: number, size and location of lesions detected.
- To evaluate diagnostic information using lesion visualization variables (lesion border delineation, internal morphology and degree of contrast enhancement).
- To evaluate diagnostic confidence.
- To compare overall diagnostic preference between P03277 and MultiHance®.
- To assess P03277 dose/response relationship for CNR and lesion visualization variables.
- To evaluate the impact of P03277 and MultiHance®-enhanced MRI on subject treatment plan.
- To assess the safety profile of P03277 as compared to MultiHance® after intravenous administration.

1.2. Study design

Design: GDX-44-004 is a Phase IIb, multicenter, double-blind, randomized, controlled, parallel dose groups, cross-over design with comparator.

Centers: worldwide study involving 28 active centers.

Study arms:
Two subsets of subjects:

- Subset 1: first subject of each study center randomized 1:1 as follows.
    a. 0.05 or 0.1 mmol/kg Body Weight (BW) of P03277 then 0.1 mmol/kg of MultiHance® (1:1).
    b. 0.1 mmol/kg of MultiHance® then 0.05 or 0.1 mmol/kg BW of P03277 (1:1).
- Subset 2: all subsequent subjects randomized 1:1 as follows.
    a. 0.025, 0.05, 0.1 or 0.2 mmol/kg BW of P03277 then 0.1 mmol/kg of MultiHance® (1:1:1:1).
    b. 0.1 mmol/kg of MultiHance® then 0.025, 0.05, 0.1 or 0.2 mmol/kg BW of P03277 (1:1:1:1).

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

Demographic and other baseline characteristics include:

- Demographic data.
- Medical history.
- Previous medications.
- Subject intolerance to contrast agent history.
- Study disease diagnosis.
- Physical examination.
- Pregnancy test.
- Local serum creatinine and estimated Glomerular Filtration Rate (eGFR).
- MRI examination.

2.2. Efficacy criteria

2.2.1. Primary criterion

The primary criterion (off-site readings) is calculated by subject, and by independent blinded reader in a centralized procedure (off-site readers), in averaging the CNR for maximum 3 enhanced lesions. For the primary analysis, only lesions detected by both MRIs after lesion tracking will be used.

CNR is a variable derived for each lesion, from the Signal Intensity (SI) measurement. CNR will be calculated according to the following formula:

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

where SI_{lesion} = the SI in the Region Of Interest (ROI) in the lesion.
SI_{ht} = the SI in the ROI in healthy tissue (brain or spinal cord).
SD_{noise} = Standard Deviation (SD) of background noise.

2.2.2. Secondary efficacy criteria

Secondary efficacy criteria include:

- Technical adequacy of images (off-site and on-site readings): yes or no and reason if no (1 = Artefacts due to subject, 2 = Artefacts due to machine, 3 = Artefacts due to contrast agent, 4 = Injection technical failure, 5 = Other, specify).

- Lesion detection capacity: number of enhancing lesions (off-site and on-site readings) and number of lesions detected (off-site readings only); for the 3 most representative lesions: size of lesions (largest diameter), location of lesions and presence or absence of contrast enhancement (off-site and on-site readings). Contrast enhancement is absent if the degree of contrast enhancement is 1 = No: no enhancement and present if it is 2 = Moderate: weakly enhanced, 3 = Good: clearly enhanced or 4 = Excellent: clearly and brightly enhanced.

- Lesion visualization variables: lesion border delineation, visualization of lesion internal morphology and degree of lesion contrast enhancement assessed on 4-point scales (off-site and on-site readings).

  Lesion border delineation: 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.

  Visualization of lesion internal morphology: 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 lesion contrast enhancement: 1 = No: no enhancement, 2 = Moderate: weakly enhanced, 3 = Good: clearly enhanced, 4 = Excellent: clearly and brightly enhanced.

- Radiological diagnosis and level of diagnostic confidence (off-site and on-site readings).

  Radiological diagnosis is assessed according to the 9 following categories: 1 = Glial tumor, low grade (I/II), 2 = Glial tumor, high grade (III/IV), 3 = Glial tumor, tumor grade cannot be determined, 4 = Meningioma, 5 = Brain metastasis, 7 = Stroke, 8 = Abscess, 9 = Other (to be specified), 0 = Not assessable.

  Level of diagnostic confidence is assessed on a 5-point scale: 1 = Nil: very uncertain, 2 = Poor: uncertain, 3 = Moderate: moderately certain, 4 = High: good certainty, 5 = Excellent: very certain.

- Overall diagnostic preference and reason (off-site readings).

  Overall diagnostic preference is assessed on a 3-point scale: 1 = Examination 1 is preferred to examination 2, 0 = No preference is observed, 2 = Examination 2 is preferred to examination 1.

  Reason may be one or more of the 6 following ones: Contrast enhancement was superior, Delineation of normal structure was better, Delineation of at least one lesion was better, Internal structure of lesions was better visualized, More lesions were identified, Diagnostic confidence was greater (reason(s) to be specified).

- Impact on subject treatment plan (on-site reading): "could it be changed?" yes, no or no opinion and detail if yes (surgery, biopsy, chemotherapy, radiotherapy or other treatment to be specified).

2.3. Safety criteria

Safety criteria include:

- Study contrast agent administration modalities.
- Adverse Events (AEs).
- Hematology, biochemistry and urinalysis.
- ElectroCardioGram (ECG) and vital signs.
- Injection site tolerance and subject pain evaluation.
- Concomitant medications.

2.4. Other criteria

Not applicable.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed by Inferential under the supervision of Benoit Piednoir, Guerbet biostatistician, on the basis of the present document. A quality control of the statistical analysis will be performed to ensure the reliability of the results.

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

Tabulations of quantitative parameters will include the following summary statistics: number of subjects, mean, SD, minimum, median and maximum. 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.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing recorded categories.

For safety analyses, the baseline value will be defined as the last available value prior to administration of the Investigational Medicinal Product (IMP). For the primary analysis of the primary efficacy criterion, the baseline value will be the pre CNR measurement for unenhanced lesions for each contrast agent period.

All statistical tests will be performed at the significant threshold of 2.5% one-sided. P-values will be displayed with 4 decimal places.

SAS® version 9.2 will be used for all descriptive summaries and inferential analyses.

3.2. Null and alternative hypothesis

Stating the following notations:

- μ_i is the expected average of CNR of enhanced lesions for each dose of P03277 (where i is corresponding to one dose of P03277).
- μ_0 is the expected average of CNR of enhanced lesions for corresponding MultiHance® group.

Statistical hypotheses for the primary analysis of the primary criterion are:

Null hypothesis
H_i: $\mu_i - \mu_0 \leq 0$, i = 1…4

Alternative hypothesis
K_i: $\mu_i - \mu_0 > 0$, i = 1…4

3.3. Determination of sample size

Based on the hypothesis below, a total of 280 subjects were to be enrolled in the study:

- Subset 1: maximum 40 subjects (depending of the number of participating sites) on the basis of 1 subject per site.
- Subset 2: minimum 240 subjects based on the following assumption: the study aims at detecting a minimum of 30% increase of CNR for at least one of the four tested dose of P03277 compared to control arm MultiHance® at dose of 0.1 mmol/kg BW. A sample size of 50 evaluable subjects per group was required to obtain a power of at least 90%, using a t-test of a normal mean difference with a one-sided significance level of 0.025 (Holm's step-down method in a multiple comparisons design [1]) and a common SD of 3.01. Therefore, a minimum of 50 evaluable subjects per dose group and a minimum of 200 evaluable subjects in total would have to be enrolled in this study.

An evaluable subject was defined as a randomized subject, 2 contrast agents administered, having undergone 2 complete, assessable and interpretable MRI examinations, presenting with at least one enhancing lesion of minimum 5 mm (long axis).

It was anticipated that some of the subjects would not complete both MRI evaluations. To offset this, an additional 10 subjects per group were added to the 50 required leading to a total of 240 randomized subjects.

The number of non-evaluable subjects was monitored to assess the necessity for a sample size increase. The decision to increase the sample size would be made by the sponsor when approximately 80% of the planned 240 randomized subjects were enrolled. The actual rate of drop-out subjects was considered to assess the new number of subjects to be enrolled.

Subjects with brain metastasis were randomized at a minimum of 20% of the second subset of subjects. Randomization was stratified within brain metastasis (yes/no) in order to prevent unequal contrast agent allocation.

3.4. Adjustment for covariates

The pre CNR measurement for unenhanced lesions (baseline value) will be included as covariate in the statistical models for the primary and supportive analyses of the primary criterion.

The stratification factor (brain metastasis at screening) will not be included as covariate in the statistical models. Indeed, it was judged as having no impact on the primary criterion. However, the analysis of number of lesions will be provided only on the subset of subjects with brain metastasis at screening.

3.5. Handling of dropouts or missing data

3.5.1. Efficacy Analyses

No imputation will be performed in this study. Mixed models will be performed only on subjects with both MRIs: on Per Protocol Set (PPS) and on Full Analysis Set (FAS) from which only subjects whose the criterion

of interest is available at both MRIs will be selected. The mention "Subjects Having Undergone the Two MRI" will be subtitled to the relevant tables and figures for the FAS.

3.5.2. Missing and Partially Known Dates (Except AE Start Dates)

Unless otherwise specified, partially known dates will be defined as follows for duration computation:

Partially known start date

- If only the day is missing, it is estimated as the first day of the month or day of the first date in the study if it is the same month and year.
- If month and day are missing, they are estimated as January 1 or day and month of the first date in the study if it is the same year.

Partially known end date

- If only the day is missing, it is estimated as the last day of the month or day of the last date in the study if it is the same month and year.
- If month and day are missing, they are estimated as December 31 or day and month of the last date in the study if it is the same year.

The original dates without estimation will be presented in the listings.

General rules for calculating the durations

- Durations calculated in minutes: if any one of the times from the start and end "datetimes" used for the calculation of the duration is/are missing, the duration is missing.
- Durations calculated in days: if any one of the times from the start and end "datetimes" used for the calculation is/are missing, the date part of the datetime will be used to compute the duration.

3.5.3. Missing and Partially Known AE Start Dates

If an AE start date is missing or unknown, the AE will be considered as treatment emergent.

When the start date of an AE is only partially known, it will be categorized as not emergent or emergent using the following rules:

- If the partial start date is before (<) the injection at the 1st MRI procedure visit date (i.e., year or year & month is/are before those of the date of the injection) then the AE is not emergent.
- If the partial start date is after (≥) the injection at the 1st MRI procedure visit date (i.e., year or year & month is/are the same as or after those of the date injection) then the AE is emergent.

3.5.4. Missing Codes for End Date of Concomitant Medication

In case of missing code for end date of a concomitant medication, it will be replaced by the code 2 = "Between first and second IMP administration", so that the medication will be considered as concomitant (see Sections 5.4.7 and 5.6.6).

3.6. Interim analyses and data monitoring

No interim analysis is planned.

3.7. Multicenter studies

Twenty-eight (28) active centers are involved worldwide in the study, the center factor will not be included in the multivariate models for efficacy. The number of subjects included in each center will be displayed in a disposition table. Furthermore, the primary criterion will be tabulated by center without statistical inference.

3.8. Multiple comparisons/Multiplicity

A global one-sided α level of 0.025 will be guaranteed for the primary analysis of the primary criterion by use of the Holm's step-down method [1].

3.9. Use of an "efficacy subset" of subjects

Some efficacy analyses will be performed on the following subsets of the FAS:

- The PPS.
- The PPS restricted to subjects with ROI similarly placed in MRI 1 and MRI 2.
- The FAS restricted to subjects with an available criterion of interest at both MRIs.
- The FAS restricted to subjects with an available criterion of interest at both MRIs and with presence of brain metastasis.

3.10. Active control studies intended to show equivalence

Not applicable.

3.11. Examinations of subgroups

- Descriptive analyses of the primary criterion will be performed by center and by magnetic field.
- Descriptive analyses of the number of enhancing lesions (secondary efficacy criterion) will be performed by presence or absence of brain metastasis (stratification factor).

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

The protocol was amended on one occurrence. See amended protocol for a full list of changes.

RATIONALE FOR ANY DEVIATION FROM PRE-SPECIFIED ANALYSIS PLAN PERFORMED

It was planned in the protocol to repeat on the PPS the evaluation of secondary efficacy criteria in case of a difference from the FAS by more than 15%. It has been decided that only the analyses of data from off-site readings for some relevant secondary criteria will be repeated on the PPS.

Further, three secondary criteria have been added since the last amendment: The Contrast-to-Noise Ratio calculated based on the noise issued from the CerebroSpinal Fluid (CSF): CNR_{CSF}, the Lesion-to-Brain Ratio (LBR) and the Contrast enhancement percentage. The three criteria are calculated by subject, and by independent blinded reader in a centralized procedure (off-site readers) and the result is provided by exam for each reader by averaging the parameter for maximum 3 enhanced lesions.

CNR_{CSF} is derived for each lesion, from the SI measurement, according to the following formula:

$$\text{CNRcsf} = \frac{SIlesion - SIht}{SDnoise}$$

where SI_{lesion} = the SI in the ROI in the lesion.
SI_{ht} = the SI in the ROI in healthy tissue (brain or spinal cord).
SD_{noise} = SD of CSF noise.

LBR is derived for each lesion, from the SI measurement, according to the following formula:

$$\text{LBR} = \frac{SIlesion}{SIht}$$

where SI_{lesion} = the SI in the ROI in the lesion.
SI_{ht} = the SI in the ROI in healthy tissue (brain or spinal cord).

Contrast enhancement percentage is derived for each lesion, from the SI measurement, according to the following formula:

$$Contrast\ Enhancement\ Percentage = \frac{SI_{post} - SI_{pre}}{SI_{pre}}$$

where SI_{post} = the SI in the ROI in the lesion post contrast media administration.
SI_{pre} = the SI in the ROI in the lesion pre contrast media administration.

These three criteria will be analyzed as the primary criterion.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of subjects

The following descriptions (number and percentage of subjects) will be performed with regards to the disposition of subjects:

- Subject overall disposition on the Extended Set for each subset separately:
    - Subjects present at each study visit by contrast agent, sequence and globally.
    - Subjects screened, subjects randomized, subjects administered at the first MRI procedure, subjects administered at the second MRI procedure and subjects who completed the study by contrast agent, sequence and globally.
    - Subjects screen failure, reasons of screen failure, premature discontinuation from the study before receiving the 1st and the 2nd contrast agent and reasons why subjects were prematurely discontinued by contrast agent, sequence and globally.
- Subjects globally recruited in each center sorted by country on the Extended Set.

The tables that will be displayed are detailed in Section 6.1.1.1 and the listings in Section 6.2.1.

5.2. Data Sets Analysed and protocol deviations

5.2.1. Data Sets Analysed

There will be four subject sets defined for this study: the Extended Set, the Safety Set, the FAS and the PPS.

The Extended Set will include all subjects having signed the Informed Consent Form (ICF). This set will be used for subject disposition summaries, overall summary of AEs and individual listings.

The Safety Set will include all subjects, receiving at least one injection of contrast agent, regardless of the quantity. Subjects of subset 1 will be included in this set. This set will be used for description of demographic data, medical history, previous treatments and evaluation of safety. Analyses using the Safety Set will be based on the contrast agent actually received.

The FAS will include all subjects from subset 2 who have a CNR from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader. This set will be used for description of demographic data, baseline characteristics data, medical history, previous treatments and evaluation of efficacy. Analyses using the FAS will be based on the contrast agent allocated by the randomization whatever the contrast agent actually received, following the Intention To Treat (ITT) principle.

The PPS will be a subset of the FAS and will include all subjects who have no major protocol deviations (see below) throughout their whole study period. This set will be used for the evaluation of the primary efficacy criterion and main secondary criteria.

Analysis data sets will be presented on the Extended Set: subjects included in the Safety Set by contrast agent actually received and globally and included in the FAS and in the PPS by contrast agent allocated by the randomization and globally.

The tables and the listing that will be displayed are detailed in Sections 6.1.1.3 and 6.2.3.

5.2.2. Protocol Deviations

As per International Conference on Harmonization (ICH) E3 guideline [2], 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 subject safety or the efficacy assessments. Protocol deviations are displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. The list of protocol deviations is presented in the table below and can be updated if necessary before breaking the blind. Protocol deviations will be gathered from monitoring files, clinical database and external vendors of off-site data (imaging, laboratory data, ECG…).

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 categorisation is done in this document, then final categorisation will be done before breaking the blind. The decision will be duly described in the meeting minutes.

The deviations are listed in the table below:

Category	Description	Source	Status
Inclusion criteria not met/Non inclusion criteria met	Subject **not** having reached legal majority age	Clinical data base	Non major
	Subject **not** presenting, at the time of inclusion, with known or highly suspected focal areas of disrupted Blood Brain Barrier (BBB) (e.g., primary and secondary tumors, focal inflammatory or demyelinating disorders) including at least one expected enhancing lesion of minimum 5 mm (long axis). This lesion must have been detected on a previous imaging procedure (computerized Tomography (CT) or MRI)	Clinical data base	**Major**
	Subject **not** scheduled for a routine CNS contrast-enhanced MRI examination for clinical reasons **or not** agreeing to have a second contrast-enhanced MRI examination for the purpose of the study	Clinical data base	Non major
	Subject **not** able **or not** willing to participate to the study	Clinical data base	Non major
	Subject **not** having provided his/her consent to participate in writing by dating and signing the informed consent prior to any study related procedure being conducted	Clinical data base	Non major

	Subject **not** affiliated to national health insurance according to local regulatory requirements	Clinical data base	Non major
	Subject presenting with acute or chronic Grade III (at least) renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m² based on two eGFR assessments, one within 7 days before the first study MRI and one the day of the MRI (if any of the eGFR result is < 60 mL/min/1.73m², the subject is not eligible)	Clinical data base	Non major
	Subject presenting with known class III/IV congestive heart failure according to the New York Heart Association classification (NYHA)	Clinical data base	Non major
	Pregnant or breast-feeding female subject (a female subject of childbearing potential or with amenorrhea for less than 12 months must have a negative urine or serum pregnancy test within 24 hours prior to study MRI and must be using a medically approved contraception method* until the last study visit)	Clinical data base	Non major
	Subject having received any investigational medicinal product within 30 days prior to study entry	Clinical data base	Non major
	Subject previously enrolled in this study	Clinical data base	Non major
	Subject presenting with any contraindication to MRI examinations	Clinical data base	Non major
	Subject with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or other GBCAs	Clinical data base	Non major
	Subject having received any contrast agent (MRI or CT) within 3 days prior to study products administration, or scheduled to receive any contrast agent during the course of the study or within 24 hours after the second study product administration	Clinical data base	Non major
	Subject having received any treatment or medical procedure within 7 days prior to the first MRI or expected/ scheduled to have a change in any treatment or medical procedure in-between the 2 MRI examinations	Clinical data base	Non major
	Subject with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the subject's safety or her/his ability to participate in the study	Clinical data base	Non major
	Subject unlikely to comply with the protocol, e.g. uncooperative attiude, inability to return for follow-up visits and/or unlikelihood of completing the study	Clinical data base	Non major
	Subject related to the Investigator or any other study staff or relative directly involved in the study conduct	Clinical data base	Non major

	Subject presenting with acute relapse of multiple sclerosis	Clinical data base	Non major
	eGFR on local measurements below 60 mL/min/1.73m^2 at visit 2 or visit 4 and contrast media administration performed	Clinical data base	Non major
	eGFR on central measurements below 60 mL/min/1.73m^2 at visit 2 or visit 4 and contrast media administration performed	Laboratory data base	Non major
	eGFR on local measurements not performed one day before contrast media administration	Clinical data base	Non major
	eGFR on local measurements at visit 1 not performed within 7 days before first contrast media administration	Clinical data base	Non major
	eGFR method is not accurate	Clinical data base	Non major
	No pregnancy test done 1 day before contrast media administration for female of childbearing potential	Clinical data base	Non major
Study disease diagnosis	Procedure used for documenting at least one enhancing lesion is **not** provided	Clinical data base	Non major
	Time between procedure used for documenting at least one enhancing lesion and first study procedure is **greater than 12 months for Czech Republic (CZ)**	Clinical data base	Non major
Imaging	Not matching lesion: among subjects with both MRI examinations done, those without **enhancing** lesions **matching** at both examination for all off-site readers	Imaging data base	**Major**
	Scanner-related deviation from the MRI procedures	Clinical data base	Non major
	Subject-related deviation from the MRI procedures	Clinical data base	Non major
	Anatomy (Brain/Spine) is different between on-site and off-site evaluation	Clinical data base and imaging data base	Non major
	Anatomy is Brain for one period and Spine for the other one in the off-site evaluation for at least one off-site reader	Imaging data base	Non major
	Anatomy is Brain for one period and Spine for the other one in the on-site evaluation	Clinical data base	Non major
	Imaging protocol not respected with major impact on primary criterion	Monitoring	**Major**
	Imaging protocol not respected with impact on primary criterion	Monitoring	Non major

Subject not withdrawn as per protocol	Stopping rules detected on local measurements and subject not withdrawn: Increase in serum creatinine by more than 25% or 0.5 mg/dL (44 umol/L) compared to the baseline value	Clinical data base	Non major
	Stopping rules detected on central measurements and subject not withdrawn: Increase in serum creatinine by more than 25% or 0.5 mg/dL (44 umol/L) compared to the baseline value	Central laboratory data base	Non major
	Stopping rules detected on central measurements and subject not withdrawn: Increase in cystatin C by more than 25% compared to the baseline value	Central laboratory data base	Non major
	Stopping rules detected on central measurements and subject not withdrawn: triplicate QTc Bazett or QTc Fridericia > 500 ms or in increase of > 60 ms over baseline	Central ECG data base	Non major
	Result of pregnancy test positive and subject not withdrawn	Clinical data base	Non major
Unblinding	Blind not maintained on site	Monitoring	Non major
	Blind not maintained at central reading level	Monitoring	**Major**
Forbidden concomitant medication	Concomitant medication taken in or medical procedure between the two MRI impacting lesion size based on investigator assessment	Clinical data base	**Major**
IMP deviation	Subject **not** allocated in the good stratification factor	Clinical data base and IWRS data base	Non major
	Subject not allocated in the good sequence	Clinical data base and IWRS data base	**Major**
	Subject having performed MRI examination but **not** administered with the IMP	Clinical data base	**Major**
	The IMP volume actually administered is different from the theoretical one from 10 to 20%	Clinical data base and IWRS data base	Non major
	The IMP volume actually administered is different from the theoretical one from more than 20%	Clinical data base and IWRS	**Major**
	Location of IMP injection site is **not** adequate	Clinical data base	Non major
	Actual IMP injection rate is **not** adequate	Clinical data base	Non major
	Temperature excursion for IMP	Monitoring	Non major
	IMP management not appropriate	Monitoring	Non major
	Extravasation	Clinical data base	**Major**
Missing data	Date of birth is missing	Clinical data base	Non major
	Sex is missing	Clinical data base	Non major
	Height is missing	Clinical data base	Non major
	Race is missing	Clinical data base	Non major
	Physical examination not performed	Clinical data base	Non major
	Blood sample for central laboratory assessment not performed	Clinical data base	Non major

	Central Laboratory Biochemistry results not available	Laboratory data base	Non major
	Central Laboratory Hematology results not available	Laboratory data base	Non major
	Urinalysis not performed	Clinical data base	Non major
	Vital signs not measured	Clinical data base	Non major
	Vital sign result missing	Clinical data base	Non major
	ECG not performed/performed but not in triplicate	Clinical data base	Non major
	ECG result missing	Central ECG data base	Non major
	Tolerance at injection site is not filled in for patient receiving the study product	Clinical data base	Non major
	No VAS completed in case of injection site pain	Clinical data base	Non major
Non respect of study's schedule and procedures	MRI examination **not** performed	Clinical data base	**Major**
	Time between the two MRI procedures is strictly greater than 14 days and less or equal to 21 days	Clinical data base	Non major
	Time between the two MRI procedures is strictly greater than 21 days	Clinical data base	**Major**
	Time between contrast media administration and 3-D GRE acquisition for Brain and T1WSE/TSE acquisition for spine is greater than 10 minutes	Clinical data base	Non major
	Two different MRI system manufacturer used for both assessments	Imaging data base	Non major
	Two different MRI system model used for both assessments	Imaging data base	Non major
	Two different MRI system software version used for both assessments	Imaging data base	Non major
	Two different magnetic field strength used for both assessments	Imaging data base	Non major
	Two different MRI machines used for both assessments	Monitoring	Non major
	MRI machine used not qualified	Monitoring	Non major
	MRI exam for subject of subset 2 performed prior investigator's qualification	Monitoring	Non major
	Time between contrast media administration and 3-D GRE acquisition for Brain and T1WSE/TSE for spine acquisition is different of more than 10 minutes but less than 30 minutes between the two MRI for a single patient	Clinical data base	Non major
	Time between contrast media administration and 3-D GRE acquisition for Brain and T1WSE/TSE for spine acquisition is different of more than 30 minutes between the two MRI for a single patient	Clinical data base	**Major**
	Time between screening visit and first contrast media administration is strictly greater than 7 days	Clinical data base	Non major

	Prior to MRI blood sample for central laboratory assessment is not drawn before contrast media administration	Clinical data base	Non major
	Prior to MRI urinalysis is not performed before contrast media administration	Clinical data base	Non major
	1 day post MRI blood sample for central laboratory assessment is not drawn the day after contrast media administration	Clinical data base	Non major
	1 day post MRI urinalysis is not performed the day after contrast media administration	Clinical data base	Non major
	Before injection vital sign is not taken before contrast media administration	Clinical data base	Non major
	45-minute after injection vital sign is not taken between 30 and 60 minutes after contrast media administration	Clinical data base	Non major
	Between 2 and 4 hours after injection vital sign is not taken between 2 and 4 hours after contrast media administration	Clinical data base	Non major
	1 day post MRI vital sign is not taken the day after contrast media administration	Clinical data base	Non major
	Before injection ECG is not performed before contrast media administration	Clinical data base	Non major
	45-minute after injection ECG is not performed between 30 and 60 minutes after contrast media administration	Clinical data base	Non major
	Between 2 and 4 hours after injection ECG is not performed between 2 and 4 hours after contrast media administration	Clinical data base	Non major
	1 day post MRI ECG is not performed the day after contrast media administration	Clinical data base	Non major
GCP deviation	ICF deviation	Monitoring	Non major
	Source document management not appropriate	Monitoring	Non major

Subjects presenting at least one protocol deviation with a status major will be excluded from the PPS.

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

Subjects with major protocol deviations throughout the study causing exclusion from the PPS will be presented by contrast agent and globally on the Extended Set for each subset separately: subjects with at least one major protocol deviation and subjects with each major protocol deviation. Non major protocol deviations will follow the same disposition.

The tables and listings that will be displayed are detailed in Sections 6.1.1.2 and 6.2.2.

5.3. Measurements of study drug compliance

The subject's theoretical dose of contrast agent calculated for each subject was given by Interactive Web Response System (IWRS). The subject's actual dose administered was recorded in the electronic Case Report Form (eCRF). When the actual dose was different from the theoretical dose, the reason had to be given and recorded in the eCRF. Subjects with a difference between theoretical and actual volumes of study product will be described using the FAS. The difference in mL and in % will be presented for these subjects by descriptive statistics. The reasons of the differences will be listed only.

The table and the listing that will be displayed are detailed in Sections 6.1.1.6 and 6.2.5.

5.4. Demographic and Other Baseline Characteristics

Demographic data will be described using the FAS, the PPS and the Safety Set, medical history and previous medications will be described using the FAS and the Safety Set whereas other baseline characteristics will be described using the FAS only.

For tables described on the FAS (and the PPS if any, see Section 5.2.1), 5 columns will be displayed: "P03277 0.025 mmol/kg", "P03277 0.05 mmol/kg", "P03277 0.1 mmol/kg", "P03277 0.2 mmol/kg" and "Total", the dose being the one allocated by the randomization (either at the 1st or the 2nd period).

For tables described on the Safety Set, 7 columns will be displayed: "P03277 0.025 mmol/kg", "P03277 0.05 mmol/kg", "P03277 0.1 mmol/kg", "P03277 0.2 mmol/kg", "Total P03277", "MultiHance®" and "Total", the dose being the one actually received (either at the 1st or the 2nd period). It corresponds to the disposition of safety tables, except for tables of AEs in which period (MRI 1 and MRI 2) will appear also.

5.4.1. Demographic data

Demographic characteristics collected at screening, except for weight at Visit 2 and Visit 4, include the following parameters:

- Age (years) calculated using the following formula: (inclusion visit date - birth date) / 365.25.
- Gender: Male; Female.
  - If Female, contraceptive status: Woman of childbearing potential using effective contraception; Post-menopausal (with minimum 12 months of amenorrhea); Surgically sterilized.
- Weight at Visit 2 and Visit 4 (kg).
- Height (cm).
- Body Mass Index (BMI) at Visit 2 and Visit 4: $BMI = \frac{BodyWeight(Kg)}{Height(m)^2}$

  where height is in m and weight in kg. BMI will be displayed as a quantitative variable only.
- 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.

The tables and the listing that will be displayed are detailed in Sections 6.1.1.4 and 6.2.4 respectively.

5.4.2. Study disease

Study disease is assessed by the imaging procedure documenting the study disease, the presence of brain metastasis or not and the diagnosis.

The most recent imaging procedure documenting at least one enhancing lesion with a size of minimum 5 mm will be described: Computed Tomography (CT), MRI, other. Time from this procedure to the first injection of contrast agent will be presented in months: (injection date - procedure date) / 30.4.

Presence of brain metastasis will be described.

Study disease diagnosis will be coded in Primary System Organ Class (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 20.1. The table will be sorted by descending global frequencies of SOC and by descending global frequencies of PT within each SOC and presented by presence of brain metastasis or not.

The tables and the listing that will be displayed are detailed in Sections 6.1.1.4 and 6.2.4 respectively.

5.4.3. Risk factors

Not applicable.

5.4.4. Medical history and concomitant diseases

Medical history collected at screening visit will be classified as follows:

- **Past diseases** are defined as diseases which are not “ongoing” at the time of the assessment of the subject’s medical history.
- **Concomitant diseases** are defined as diseases which are “ongoing” at the time of the assessment of the subject’s medical history.

Medical history will be coded in Primary SOC and PT using the MedDRA dictionary version 20.1. Data on medical history recorded at screening visit will be summarized according to SOC and PT.

The table will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT.

The tables and the listing that will be displayed are detailed in Sections 6.1.1.4 and 6.2.4 respectively.

5.4.5. Clinical laboratory evaluation at baseline

Serum creatinine and eGFR locally analyzed at Visit 2 and Visit 4 will be described as baseline characteristics using the Safety Set. These parameters will be described as quantitative variables in both Standard International (SI) and conventional (i.e. United States) units. Numbers and percentages of subjects with a value of eGFR < 60 mL/min/1.73m² will also be presented.

Serum creatinine and eGFR locally analyzed at Visit 1 will be only listed.

Hematology and biochemistry parameters centrally analyzed before the 1st injection of contrast agent will be presented as part of safety analysis (see Section 5.6.4) along with those collected after. Urinalysis data will be listed only.

The tables and the listing that will be displayed are detailed in Sections 6.1.1.4 and 6.2.4 respectively.

5.4.6. Vital signs, physical findings and other observations related to safety at baseline

ECG and vital signs data measured before the 1st injection of contrast agent will be presented as part of safety analysis (see Section 5.6.5).

5.4.7. Prior therapies

Previous medications are medications ended before the first administration of contrast agent. They correspond to medications with the category of end period: 1 = “Before first IMP administration”.

Subject’s previous medications will be coded using the World Heath Organization (WHO) Drug dictionary version B3 WHO DDE sept 2017. The number and percentage of subjects who took concomitant medications ended before the first administration of contrast agent 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).

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

The tables and the listing that will be displayed are detailed in Sections 6.1.1.4 and 6.2.4 respectively.

5.4.8. Other baseline characteristics

Other baseline characteristics collected are subject intolerance to contrast agent history, physical examination, pregnancy test and MRI examination.

5.4.8.1 Subject Intolerance to Contrast Agent History

Subject intolerance to contrast agent history at screening includes the following parameters:

- Previous intolerance due to contrast agent: Yes; No.
- If yes, Type of product (multiple choices): Gadolinium complex; Iodinated contrast agent; Barium; Diagnostic radiopharmaceutical; Other.

These data will be displayed in a listing only (see Section 6.2.4).

5.4.8.2 Physical Examination

These data will be displayed in a listing only (see Section 6.2.4).

5.4.8.3 Pregnancy Test

These data will be displayed in a listing only (see Section 6.2.4).

5.4.8.4 MRI Examination

MRI examination at Visit 2 and Visit 4 includes the following parameters:

- MRI performed: Yes; No.
- If yes:
    - Time between the injection of contrast agent and T1 post-injection sequence (minutes) calculated for each of the MRI procedure using the following formula: Date/time of the T1 post-injection - Date/time of the injection of contrast agent.
    - MRI examination: Brain; Spine.
    - Magnetic field strength: 1.5 Tesla (T); 3.0T. Any other value will be considered as missing.

Descriptive statistics for MRI examination will be presented by contrast agent using the FAS. The occurrence of any deviation from the MRI procedures (Yes; No; If yes, Specification (multiple choices): Scanner-related deviation; Subject-related deviation) and the anatomy, that is to say the MRI examination as per central readers, will be only listed.

The table and the listing that will be displayed are detailed in Sections 6.1.1.5 and 6.2.5 respectively.

5.5. Efficacy evaluation

Listing of all efficacy data will be presented in CSR appendix 16.2.6.

5.5.1. Primary analysis of the primary criteria

The primary objective of the study is to determine a safe and effective dose of P03277 based on a comparison of CNR between several doses, 0.025, 0.05, 0.1 and 0.2 mmol/kg of P03277 and MultiHance® at 0.1 mmol/kg.

The primary criterion is the CNR calculated from the SI measurement of maximum 3 enhanced lesions by the 3 independent blinded readers. CNR averaged for matching lesions per subject will be used in the primary analysis.

The primary analysis will test differences of means of primary criterion for each dose of P03277 compared to MultiHance® and will be done for each of the 3 independent blinded readers (off-site) using the PPS. Holm's step-down method [1] will be used to address multiplicity testing considering the 4 contrast agents to be tested.

A subject will be analyzed as soon as he has a matching evaluation of the CNR at both MRIs by at least one off-site reader. Therefore the numbers of subjects analyzed by reader may be different.

5.5.1.1 Statistical Hypothesis for the Primary Analysis

For each of the 3 readers and each dose of P03277 (4 doses), a mixed model for correlated data will be done for assessing the primary criterion. Factors included in the 12 different models are contrast agent (P03277 and MultiHance®) and the pre contrast CNR measurement (baseline).

Differences between means for each contrast agent *versus* MultiHance® will be tested according to the following items:

- μ_i is the expected average of CNR of enhanced lesions for each dose of P03277 (where i is corresponding to one dose of P03277).
- μ_0 is the expected average of CNR of enhanced lesions for corresponding MultiHance® group.

Null hypothesis
H_i: $\mu_i - \mu_0 \leq 0$, i = 1…4

Alternative hypothesis
K_i: $\mu_i - \mu_0 > 0$, i = 1…4

For each contrast agent, the p-value for comparing the doses of P03277 with corresponding MultiHance® is calculated for testing above hypotheses and the associated 95% two-sided Confidence Interval (CI) is provided.

5.5.1.2 Holm's Step-Down Method

Let p_1, p_2, p_3 and p_4 be the ordered p-values (from the lower to the upper value) and H_1, H_2, H_3 and H_4 be the corresponding ordered null hypothesis. The testing procedure starts with the most significant comparison and

continues as long as tests are significant (meaning that the alternative statistics is met). The procedure stops the first time a non-significant comparison occurs and all remaining hypotheses will not be tested.

In the first step, H_1 is rejected if $p_1 \leq \alpha/4$, in the second step (if any) H_2 is rejected if $p_2 \leq \alpha/3$, in the third step (if any), H_3 is rejected if $p_3 \leq \alpha/2$ and in the fourth and last step, H_4 is rejected if $p_4 \leq \alpha$, with α being the one-sided significance level of 0.025.

The models will include the contrast agent group, the period and the unenhanced value as baseline data. The parameters of the mixed models will be estimated using the SAS® procedure Mixed. The difference between contrast agent groups in mean score and associated 95% two-sided CI will be computed.

5.5.1.3 SAS® Procedure

The SAS® procedure used for the primary analysis of the primary criterion will be the following:

```
proc mixed data = XXX method = REML;
  class subject trt period;
  model eval = trt period baseline;
  random subject / type = cs;
  lsmeans trt / pdiff = controlu('MultiHance') tdiff cl alpha = 0.025;
  /* The following code is needed as previous statement lsmeans does not provide the upper limit of CI */
  lsmeans trt;
  estimate "P03277 - MultiHance" trt 1 -1 /cl;
run;
```

A plot of Least Squares (LS) means from the mixed models for correlated data will be designed. The figure will display the doses on X axis and the difference *versus* MultiHance® on Y axis

5.5.1.4 Validation of Statistical Model

The validation of the statistical model used for the primary analysis will be done through graphical method. A normal Quantile-Quantile (Q-Q) plot will be drawn for each off-site reader. If we observe visually a strong deviation from normality hypotheses, alternative methods can be proposed to fit more appropriately the data distribution (log transformation, non-parametric analyses, …).

5.5.1.5 Selection Basis for Clinical Dose

The clinical dose will be selected according to the clinical benefit/risk ratio among the four doses evaluated based on the primary and secondary efficacy criteria analyzed in this study. A dose of P03277 which is not proved to be superior to the comparator on the primary criterion could however be recommended for use.

The table and the figures that will be displayed are detailed in Section 6.1.2.1.1 and the listings in Section 6.2.6.1.

5.5.2. Supportive analyses of primary criterion

5.5.2.1 FAS Analysis

The primary analysis will be repeated using the FAS. However, this analysis will be restricted to subjects with CNR data at both MRIs. It will avoid the mixed model to impute any missing CNR data. All lesions will be considered, including not matched lesions, on the contrary to the primary analysis. Lesions not matching between both MRIs will therefore be included in this supportive analysis.

The table and the figure that will be displayed are detailed in Section 6.1.2.1.2.

5.5.2.2 Overall Analysis

The primary analysis will be repeated using the PPS for matching lesions only and considering in the same model data from the 3 off-site readers. The reader factor will be included in the model and repeated by subject.

For each dose of P03277 SAS® procedure used for this analysis will be the following:

```
proc mixed data = XXX method = REML;
  class subject trt period reader;
  model eval = trt period baseline reader trt*reader;
  random subject / type = cs;
  lsmeans trt / pdiff = controlu('MultiHance') tdiff cl alpha = 0.025;
  lsmeans trt;
  estimate "P03277 - MultiHance" trt 1 -1 /cl;
run;
```

The table that will be displayed is detailed in Section 6.1.2.1.2.

5.5.2.3 Descriptive Statistics

Results of CNR from both unenhanced and contrast enhanced SI measurements will be presented at subject level (mean by subject) for each off-site reader and each dose of P03277 by period and combined periods 1 and 2 according to the contrast agent group.

By-site summaries will be produced to look for potential disparities among the sites (center effect). The presentation will be limited to descriptive statistics of contrast enhanced SI measurements in total. The p-values will not be reported for the by-site summaries.

Descriptive statistics of CNR from contrast enhanced SI measurements in total will be presented at subject level (mean by subject) for each off-site reader according to the contrast agent group and magnetic field: 1.5T or 3.0T.

Every descriptive analyses will be performed using the FAS restricted to patients with CNR data at both MRIs. Global descriptive statistics will be performed also using the PPS for matching lesions only.

The tables that will be displayed are detailed in Section 6.1.2.1.2.

5.5.2.4 Sensitivity Analysis on Subjects With Region of Interest Similarly Placed in MRI 1 and MRI 2

The primary analysis will be repeated per reader using the PPS for matching lesions only on lesions with ROI similarly placed in MRI 1 and MRI 2 according to the lesion tracker.

The table that will be displayed is detailed in Section 6.1.2.1.2.

5.5.3. Additional analyses of primary criterion

5.5.3.1 Dose/Response Relationship

The relationship between doses and CNR will be explored by two modeling approaches on all data observed under P03277. On the contrary to previous analyses, all subjects from the FAS with data under P03277 will be taken into account in the analysis, even if they had no MultiHance® in MRI 2. The following models will be performed considering the dose as a continuous variable:

- The *linear model* whose use is justified by the fact that it is the easiest approach needing no *a priori* knowledge of the pattern of relationship between dose and response.
- The E_{max} *model*, linear in log-dose, which may also be adequate based on existing data of CNR with P03277.

These analyses will be performed for the 3 off-site readers independently.

The linear model fits the dose/response function g(dose) according to the following formula:

g(dose) = E0 + δ * dose, where E0 is the response at baseline (i.e., absence of dose) and δ is a slope factor.

The SAS® procedure used for these analyses will be the following:

```
proc reg data=XXX;
  model eval =dose;
  output out=XXX predicted=xx;
run;
```

The 4-parameter E_{max} model fitting the dose/response function g(dose) according to the following formula will be used:

$g(dose) = E0 + (Emax * dose^{\lambda}) / (ED50^{\lambda} + dose^{\lambda})$

where E0 is the response at baseline (i.e., absence of dose), Emax is the asymptotic maximum dose effect (maximum effect attributable to the contrast agent), ED50 is the dose which produces 50% of the maximal effect and λ is a slope factor.

The SAS® procedure used for these analyses will be the following:

```
proc nlin data = XXX;
  parms E0 = xxx Emax = xxx ED50 = xxx lambda = xxx;
        /* Initial parameters may be estimated based on study data; in particular, lambda may be retrieved from
           the estimated slope parameter in proc reg above */
  model eval = E0 + (Emax * dose** lambda) / (ED50** lambda + dose** lambda);
  output out=XXX predicted=xx;
run;
```

Results from these models will be displayed in tables containing estimates and in figures:

- Dose on X axis.
- CNR on Y axis.
- Adjusted line (linear model) or curve (E_{max} model).

The tables and figures that will be displayed are detailed in Section 6.1.2.1.3.

5.5.3.2 Intra- Off-Site Reader Variability

Intra-reading variability will be analyzed in a subgroup of 10% of subjects randomly selected for whom the off-site readers have re-read the images.

Intra-central reader variability will be studied by a Bland-Altman graph [3]:

- Average of 1st and 2nd reading on X axis.
- Difference 2nd reading - 1st reading on Y axis.
- Horizontal lines at 0, Mean + 1.96SD and Mean - 1.96SD, where Mean and SD are the mean and the SD of the averages of 1st and 2nd readings.

One scatter plot per reader will be presented with different colors for each dose of P03277.

Descriptive statistics and the Intra-Class Correlation (ICC) [4] will also be provided. It will be based on a one-way random effect model without observed effect:

$$Y_{ijk} = \mu + \alpha_i + \varepsilon_{ijk}$$

with $\alpha_i \sim N(0,\sigma_\alpha^2)$ and $\varepsilon_{ijk} \sim N(0,\sigma_\varepsilon^2)$ and ε_{ijk} is independent of α_i.

$$ICC = \sigma_\alpha^2 / (\sigma_\alpha^2 + \sigma_\varepsilon^2)$$

which is estimated by

$$(MS_\alpha - MS_\varepsilon) / (MS_\alpha + MS_\varepsilon)$$

where MS_α and MS_ε are the mean sums of squares from the one-way ANalysis Of VAriance (ANOVA) model for between and within subjects, respectively.

SAS® procedure used for the analyses of this secondary efficacy criterion will be the following for each off-site reader:

```
ods output OverallANOVA =icc0;
proc glm data=intra;
  class patno reading;
  model BV = patno reading;
run;
data ICC;
  retain sb sw;
  set icc0 end=last;
  if source='Model' then sb=ms;
  if source='Error' then sw=ms;
  if last then do;
    ICC=round((sb-sw)/(sb+sw), 0.01);
    output;
  end;
run;
```

The analyses will be performed using the FAS.

The tables and figures that will be displayed are detailed in Section 6.1.2.1.3.

5.5.3.3 Inter- Off-Site Reader Variability

Inter-reading variability will be evaluated on the whole set of study subjects, since each case was read by 3 different readers.

The same methodology as the one presented above for intra-off-site variability will be applied. One scatter plot for each of the 3 comparisons will be presented. The factor “reader” will be used instead of the factor “reading” in the model.

The tables and figures that will be displayed are detailed in Section 6.1.2.1.3.

5.5.4. Analysis of secondary criteria

Depending on the way they were collected, the criteria will be displayed for the off-site readings and/or the on-site reading. Descriptions will be systematically done by reader. Analyses of secondary criteria will be described using the FAS only, except the first three criteria for which the PPS will be considered also (for matching lesions only).

5.5.4.1 CNR Calculated Based on Cerebrospinal Fluid

As described in the Section 4, CNR calculated based on cerebrospinal fluid (CNR_{CSF}) is added as secondary criterion. CNR_{CSF} will be analyzed as the primary criterion but limited to the following analyses: PPS analysis, FAS analysis, descriptive analysis overall and dose response.

The tables and figures that will be displayed are detailed in Section 6.1.2.2.1 and the listings in Section 6.2.6.1.

5.5.4.2 Lesion-to-Brain Ratio

As described in the Section 4, Lesion-to-Brain Ratio (LBR) is added as secondary criterion. LBR will be analyzed as the primary criterion but limited to the following analyses: PPS analysis, FAS analysis, descriptive analysis overall and dose response.

The tables and figures that will be displayed are detailed in Section 6.1.2.2.2 and the listings in Section 6.2.6.1.

5.5.4.3 Contrast Enhancement Percentage

As described in the Section 4, Contrast Enhancement Percentage is added as secondary criterion. It will be analyzed as the primary criterion without adding the pre contrast administration value in the models but limited to the following analyses: PPS analysis, FAS analysis, descriptive analysis overall and dose response.

The tables and figures that will be displayed are detailed in Section 6.1.2.2.3 and the listings in Section 6.2.6.1.

5.5.4.4 Technical Adequacy of Images

The adequacy of images was assessed by off-site readers and on-site radiologists as adequate or not and reason for inadequacy (with specification in case of other reason) recorded using a 5-items list.

Descriptive statistics for these secondary efficacy criteria will be presented by contrast agent group.

The tables and listings that will be displayed are detailed in Sections 6.1.2.2.4 and 6.2.6.2 respectively.

5.5.4.5 Lesion Detection Capacity

The *number of enhancing lesions*, the *size of the three largest representative lesions through their largest diameter* and the *location of the three largest representative lesions* by subject were assessed by off-site readers and on-site radiologists for each dose of P03277 by contrast agent.

Descriptive statistics will be presented for the largest diameter (mm) and the location of each of the three most representative lesions according to the contrast agent group and for each of the three independent off-site readers and the on-site reader.

The number of enhancing lesions and the *largest diameter of the smallest lesion detected* will be analyzed in the same way with the following specifications:

- The exact number of enhancing lesions is not collected for off-site readings in case of > 10 lesions. A conventional value of 11 will be considered for both quantitative description and modeling (see below).
- The number of enhancing lesions will be described by presence of brain metastasis or not. This disposition is justified by an expected link of this stratification factor to the number of enhancing lesions.
- If ≤ 3 lesions are detected, the smallest lesion is the one with the smallest largest diameter. If > 3 lesions are detected, the largest diameter of the smallest lesion is specifically collected.

The number of enhancing lesions will be fitted by a multivariate model also. The negative binomial distribution is more appropriate than the more standard Poisson one for modeling lesion count data (see [5] in multiple sclerosis) and will therefore be used.

The dependent variable will be the count of enhancing lesions. The model will include the factor contrast agent group and period. The model will be limited to the subjects with presence of brain metastasis which is supposed to be linked to the number of enhancing lesions. Each off-site reader will be analyzed by a specific model and on-site reading will be analyzed in the same way. The parameters of the model will be estimated using the SAS® procedure Glimmix. The difference between contrast agent groups in mean of lesions detected and associated 95% CI will be computed for each dose of P03277.

For each dose of P03277 SAS® procedure used for the analyses of this secondary efficacy criterion will be the following for each off-site reader and on-site reading:

```
proc glimmix data = XXX;
  class subject trt period;
  model eval = trt period / dist = negbin link = id;
  random _residual_ / subject = subject type = cs;
  lsmeans trt / pdiff = controlu('MultiHance') tdiff cl alpha = 0.025;
  lsmeans trt;
  estimate "P03277 - MultiHance" trt 1 -1 /cl;
run;
```

The number of lesions detected on off-site readings will be listed only.

The *absence of contrast enhancement* is defined **at lesion level** by a degree of contrast enhancement equal to 1 = no: no enhancement. The absence of contrast enhancement will be analyzed **at subject level** only by considering its absence as soon as it is absent for all lesions. It will be presented by descriptive statistics.

The tables and listings that will be displayed are detailed in Sections 0 and 6.2.6.2 respectively.

5.5.4.6 Lesion Visualization Variables

Off-site blinded readers and on-site radiologists graded the lesion visualization of the three largest representative lesions, using 3 variables (*lesion border delineation, internal morphology and degree of contrast enhancement*) assessed on a 4-point scale ranging from 1 to 4. For each variable, one subject score will be computed in adding up all lesion scores within subject by contrast agent.

The above lesion variables will lead to 3 scores **at subject level** consisting in adding up scores of lesions for each subject: border delineation sum of scores, visualization of internal morphology sum of scores and degree of contrast enhancement sum of scores.

For each of the three lesion variables, a sum of scores will be computed. Endpoints are defined based on a 4-point scale ranging from 1 to 4 for the 3 most representative lesions.

The sum of scores for each of the three variables will be calculated as follows: Sum of scores = score of the lesion number 1 + score of the lesion number 2 + score of the lesion number 3. The sum of scores for each of

the lesion endpoints will range from 0 to 12. The following rules will apply independently for each of the three variables:

- In case of absence of lesions, the sum of scores will be equal to 0.
- In case of one or two lesions only, the collected score(s) will be considered and added in case of two.
- If one score is missing for one lesion then the sum of scores will be missing.

For each dose of P03277, the two contrast agent groups will be compared using a mixed model for correlated data. Each mixed model will be performed for the three independent off-site readers and the on-site reader.

For each mixed model, the dependent endpoints will be the sum of scores of lesion border delineation, the sum of scores of visualization of lesion internal morphology and the sum of scores of degree of lesion contrast enhancement, respectively.

The models will include the contrast agent group and the period. The parameters of the mixed models will be estimated using the SAS® procedure Mixed. The difference between contrast agent groups in mean score and associated 95% CI will be computed for each dose of P03277.

Analyses using the FAS will be restricted to subjects whose the criterion of interest (lesion border delineation, internal morphology or degree of contrast enhancement) is available at both MRIs.

For each dose of P03277 SAS® procedure used for the analyses of these secondary efficacy criteria will be:

```
proc mixed data = XXX method = REML;
  class subject trt period;
  model eval = trt period;
  random subject / type = cs;
  lsmeans trt / pdiff = controlu('MultiHance') tdiff cl alpha = 0.025;
  lsmeans trt;
  estimate "P03277 - MultiHance" trt 1 -1 /cl;
run;
```

Descriptive quantitative statistics for the 3 sums of scores for border delineation, visualization of internal morphology and degree of contrast enhancement will be presented by contrast agent group for each dose of P03277.

The tables and listings that will be displayed are detailed in Sections 0 and 6.2.6.2 respectively.

5.5.4.7 Diagnostic Confidence

Descriptive statistics for the *diagnosis of the MRI* and the *level of diagnostic confidence* will be presented by contrast agent group for each dose of P03277; off-site and on-site reader's outcomes will be separately analyzed.

The tables and listings that will be displayed are detailed in Sections 6.1.2.2.7 and 6.2.6.2 respectively.

5.5.4.8 Overall Diagnostic Preference

The *level of overall diagnostic preference of images* will be displayed as follows:

- P03277 is preferred to MultiHance®.
- No difference between the 2 contrast agents.
- MultiHance® is preferred to P03277.

For each off-site reader, the overall diagnostic preference will be tabulated for each dose of P03277. Each dose of P03277 will be compared to MultiHance® by a Wilcoxon signed-rank test.

SAS® procedure used for this analysis will be:

```
proc univariate data=XXX;
  class reader dose;
  var diff;
  output out=XXX probs=PROBS;
run;
```

The *reason of this preference* (at least one among a pre-specified list of 6) will be displayed according to the contrast agent preferred.

The tables and listings that will be displayed are detailed in Sections 6.1.2.2.8 and 6.2.6.2 respectively.

5.5.4.9 Impact on Subject Treatment Plan

The impact on subject treatment plan will be assessed by on-site radiologists and will be summarized for each dose of P03277 by contrast agent group.

The table and the listing that will be displayed are detailed in Sections 6.1.2.2.9 and 6.2.6.2 respectively.

5.6. Safety Evaluation

All safety parameters will be analyzed using the Safety Set on the following contrast agent groups: “P03277 0.025 mmol/kg”, “P03277 0.05 mmol/kg”, “P03277 0.1 mmol/kg”, “P03277 0.2 mmol/kg”, “Total P03277” and “MultiHance®”. A subject will be included in a group as soon as he actually received the displayed contrast agent, either at the 1st or the 2nd period.

5.6.1. 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.

5.6.1.1 Summary of Durations in the Study

The following times will be presented by descriptive statistics:

- Between the inclusion date and the 1st injection of contrast agent (days): date of the 1st injection of contrast agent - date of signature of the ICF.
- Between the 1st and the 2nd injection of contrast agent (days): date of the 2nd injection of contrast agent - date of the 1st injection of contrast agent.
- Between the 2nd injection of contrast agent and the last study visit (days): date of the subject's last study visit - date of the 2nd injection of contrast agent.
- Between the inclusion visit and the last study visit (days): date of the subject's last study visit - date of signature of the ICF.

The table and the listing that will be displayed are detailed in Sections 6.1.3.1 and 6.2.5 respectively.

5.6.1.2 Study Contrast Agent Administration Modalities

The following parameters will be presented by descriptive statistics:

- Location of injection site: Antecubital vein; Other (to be specified).
- Theoretical volume as per IWRS (mL).
- Volume of study contrast agent actually administered (mL).
- Occurrence of an overdose: Yes; No.
- Actual injection rate (mL/s): as a quantitative variable and as a categorical variable in 3 categories (< 2 mL/s, [2 ; 3] mL/s and > 3 mL/s).
- Mode of injection: Manual; Power injector.

The following parameters will be listed only:

- Number of vials dispensed: 1; 2; 3.
- Reason why the volume actually administered is different from the theoretical calculated volume as per IWRS (free specification).

The table and the listing that will be displayed are detailed in Sections 6.1.3.1 and 6.2.5 respectively.

5.6.2. Adverse Events

AEs will be coded using MedDRA dictionary version 20.1. The time period for the assessment of AEs is the time interval between the signature of the ICF and the subject's study end. AEs will be described systematically in terms of number and percentage of subjects with AEs and in terms of number of AEs. AEs will be displayed by period (MRI 1 and MRI 2) and overall.

TEAEs will be defined as follows:

- If the AE starts prior to the 1st injection then the AE is not emergent (pre-injection).
- If the AE starts after the 1st injection, then the AE is emergent (post-injection).
    - If it starts between the 1st injection and the 2nd injection (<), then it will be considered as an emergent AE associated with the 1st contrast agent of the subject's sequence.
    - If it starts after the 2nd injection (≥), then it will be considered as an emergent AE associated with the 2nd contrast agent of the subject's sequence.

5.6.2.1 Overall Safety Summary

An overall summary of AEs will be presented using the Extended Set to catch AEs of subjects who did not receive at least one injection of contrast agent. The table will be presented with the overall "Total" column only with the following variables:

- Total number of AEs.
- Total number of subjects with at least one AE.
- Distribution of the number of AEs reported by subject (0, 1, 2 or 3 or more AEs).
- Total number of Serious AEs (SAEs) (variable "serious" classified as yes or missing).
- Total number of subjects with at least one SAE.
- Total number of AEs according to intensity.
- Total number of subjects with at least one AE according to intensity (subjects with AEs having different intensities will be counted in each category of intensity).
- Total number of AEs according to the outcome.
- Total number of subjects with at least one AE according to the outcome (subjects with AEs having different outcomes will be counted in each category of outcome).
- Total number of AEs requiring a concomitant drug (other action taken).
- Total number of subjects with at least one AE requiring a concomitant drug (other action taken).

The same table will be displayed by dose of P03277 and period for Treatment Emergent AEs (TEAEs) using the Safety Set. The terms "AE" will be replaced by "TEAE". The following variables will be also presented:

- Total number of TEAEs with causal relationship to the IMP.
- Total number of subjects with at least one TEAE with causal relationship to the IMP.
- Total number of TEAEs requiring withdrawal of study contrast agent (action taken).
- Total number of subjects with at least one TEAE requiring withdrawal of study contrast agent (action taken).

The tables that will be displayed are detailed in Section 6.1.3.2.1.

5.6.2.2 TEAEs

The number and percentage of subjects with at least one TEAE will be presented using the Safety Set by dose of P03277 and period according to Primary SOC and PT.

The table will be sorted by descending frequency of SOC and, within each SOC by descending frequency of PT.

The table that will be displayed is detailed in Section 6.1.3.2.2.

5.6.2.3 TEAEs with Causal Relationship to the IMP

The number and percentage of subjects with at least one TEAE with causal relationship to the IMP will be presented by dose of P03277 and period according to Primary SOC and PT. AEs with causal relationship to the IMP are those described by the investigator with causal relationship to the IMP "related" or as AEs with unassessable relationship.

The table that will be displayed is detailed in Section 6.1.3.2.3.

5.6.2.4 TEAEs with Causal Relationship to a Study Procedure

The number and percentage of subjects with at least one TEAE with causal relationship to a study procedure will be presented by dose of P03277 and period according to Primary SOC and PT. AEs with causal relationship to a study procedure are those described by the investigator with causal relationship to a study procedure "related" or as AEs with unassessable relationship.

The table that will be displayed is detailed in Section 6.1.3.2.4.

The listings that will be displayed on AEs and TEAEs are detailed in Section 6.2.7. They will present a complete description of the AE by Primary SOC, Lowest Level Term (LLT), PT and description, including date/time of onset, end date, duration, intensity, seriousness, causal relationship to the IMP, causal relationship to a study procedure, withdrawal of study contrast agent (action taken), concomitant drug (other action taken) and the outcome. The displayed duration of an AE will be computed in days using the following formula: event end date - date/time of onset + 1. In case one of the dates is missing or incomplete then the duration will be missing. The listings will be sorted by contrast agent group, subject number, date/time of onset, end date, Primary SOC, PT and description.

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

Deaths, if any, will be listed in Table 14.3.2.6. SAEs will be listed in Table 14.3.2.7. These listings will be sorted by contrast agent group, subject number, date/time of onset, end date, Primary SOC, LLT, PT and description.

5.6.4. Clinical laboratory evaluation

Hematology data from central laboratory include the following parameters (in SI and conventional units):

	SI units	Conventional units
Red Blood Cells (RBC) = Erythrocytes	10^{12} /L	10^{6} /µL
White Blood Cells (WBC) = Leukocytes	10^{9} /L	10^{3} /µL
Neutrophils	10^{9} /L	10^{3} /µL
Neutrophils/Total Cells	%	%
Eosinophils	10^{9} /L	10^{3} /µL
Eosinophils/Total Cells	%	%
Basophils	10^{9} /L	10^{3} /µL
Basophils/Total Cells	%	%
Lymphocytes	10^{9} /L	10^{3} /µL
Lymphocytes/Total Cells	%	%
Monocytes	10^{9} /L	10^{3} /µL

	SI units	Conventional units
Monocytes/Total Cells	%	%
Platelet count	10^9 /L	10^3 /µL
Hemoglobin	g/L	g/dL
Hematocrit	v/v	%
Mean Corpuscular Volume (MCV)	fL	fL

Biochemistry data from central laboratory include the following parameters:

	SI units	Conventional units
Sodium	mmol/L	mEq/L
Potassium	mmol/L	mEq/L
Chloride	mmol/L	mEq/L
Glucose	mmol/L	mg/dL
Blood Urea Nitrogen (BUN)	mmol/L	mg/dL
Urea	mmol/L	mg/dL
Serum creatinine	umol/L	mg/dL
eGFR	mL/min/1.73m²	mL/min/1.73m²
Total protein	g/L	g/dL
Calcium	mmol/L	mg/dL
Phosphorus	mmol/L	mg/dL
Total bilirubin	umol/L	mg/dL
Indirect bilirubin	umol/L	mg/dL
Conjugated bilirubin	umol/L	mg/dL
Aspartate Amino Transferase (AST)	U/L	U/L
Alanine Amino Transferase (ALT)	U/L	U/L
Alkaline Phosphatase	U/L	U/L
Lactate DeHydrogenase (LDH)	U/L	U/L
Triglycerides	U/L	U/L
Cystatin C	U/L	U/L

Hematology and biochemistry parameters at visits 2, 3, 4 and 5 will be described as quantitative variables in both SI and conventional units. Numbers and percentages of subjects with values out of range (lower than the lower limit or higher than the upper limit of quantification) will also be presented, except if values for normal ranges are unknown for a parameter.

Erythrocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, hemoglobin and hematocrit (hematology) and potassium, chloride, BUN, urea, total protein, phosphorus, total bilirubin, AST, ALT, alkaline phosphatase, triglycerides and cystatin C (biochemistry) will be separately described by gender.

Change from baseline in *serum creatinine, eGFR, BUN and cystatin C* will be computed and described at visits 3, 4 and 5 in both SI and conventional units. The baseline value for each laboratory parameter will be the last value measured before the contrast agent administration (i.e. the assessment prior to 1st MRI).

Shift tables presenting relative change from baseline in classes *versus* baseline in classes will be displayed for *serum creatinine, eGFR, BUN and cystatin C*.

Baseline data will be classified as follows (no baseline categories will be used for cystatin C):

SI units	Conventional units
• Serum creatinine (umol/L): o < 20 o ≥ 20 and < 40 o ≥ 40 and < 60 o ≥ 60	• Serum creatinine (mg/dL): o < 0.22 o ≥ 0.22 and < 0.44 o ≥ 0.44 and < 0.66 o ≥ 0.66
• eGFR (mL/min/1.73m²): o < 100 o ≥ 100 and < 150 o ≥ 150 and < 200 o ≥ 200	• eGFR (mL/min/1.73m²): o < 100 o ≥ 100 and < 150 o ≥ 150 and < 200 o ≥ 200
• BUN (mmol/L): o < 2 o ≥ 2 and < 4 o ≥ 4 and < 6 o ≥ 6	• BUN (mg/dL): o < 12 o ≥ 12 and < 24 o ≥ 24 and < 36 o ≥ 36

Relative change from baseline will be calculated as follows: 100* (post injection measurement - baseline measurement) / baseline measurement. Relative change from baseline will be classified as follows:

- ≤ -50%.
- > -50% and ≤ -25%.
- > -25% and ≤ -15%.
- > -15% and < 0%.
- ≥ 0% and < 15%.
- ≥ 15% and < 25%.
- ≥ 25% and < 50%.
- ≥ 50%.

Numbers and percentages of subjects in each class will be presented in both SI and conventional units for centrally analyzed data only.

Urinalysis data will be only listed.

The tables and listings that will be displayed are detailed in Sections 6.1.3.3 and 6.2.8 respectively.

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

5.6.5.1 ECG

Three values are expected at each time point (triplicate ECG): before injection, 45 (±15 minutes) after injection, between 2 and 4 hours after injection and 1 day after injection (for both injections). The value analyzed will be the mean of the non-missing values obtained from this triplicate ECG.

The QT corrected (QTc) interval will be described, separating QTc Fridericia's and QTc Bazett's. These parameters at each time point will be described as quantitative variables.

Change from baseline in ECG parameters will be computed and described at each post-baseline measurement. The baseline value will be the triplicate ECG measured prior to the injection of the 1st contrast agent.

Numbers and percentages of subjects with values out of range will also be presented, based on a notable QTc > 450 ms, a notable QTc > 500 ms and a notable QTc change from baseline > 60 ms.

Other ECG parameters than QTc will be listed only.

The tables and the listing that will be displayed are detailed in Sections 6.1.3.4.1 and 6.2.9 respectively.

5.6.5.2 Vital Signs

Vital signs were measured at 4 time points for both injections: before injection, 45 (±15) minutes after injection, between 2 and 4 hours after injection and 1 day after injection. Collected parameters were Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg) and pulse rate (beats per minute [bpm]).

Descriptive statistics for each parameter will be computed at each time point. Changes in each vital signs parameter from baseline will be computed and described by parameter. The baseline value will be the vital signs measured prior to the injection of the 1st contrast agent.

Numbers and percentages of subjects with values out of range will also be presented. Normal ranges are the following: [90; 160] mmHg for SBP, ≤ 100 mmHg for DBP and [40; 100] bpm for pulse rate.

The tables and the listing that will be displayed are detailed in Sections 6.1.3.4.2 and 6.2.9 respectively.

5.6.5.3 Injection Site Tolerance

Tolerance at the injection site was assessed at 4 time points for both injections: during injection, 45 (±15) minutes after injection, between 2 and 4 hours after injection and 1 day after injection. Occurrence or not of the following events was collected at each time point: burning, pain, eruption, extravasation, inflammation, other (to be specified). In case of pain, a subject pain evaluation was detailed through a Visual Analogic Scale (VAS) from 0 to 10 cm, with 0 being "no pain" and 10 being "maximal pain".

The above parameters will be described at each time point.

The tables and the listing that will be displayed are detailed in Sections 6.1.3.4.3 and 6.2.9 respectively.

5.6.6. Concomitant medications and procedures

Concomitant medications are medications ended after the first administration of contrast agent or ongoing at the end of the study. They correspond to medications with the categories of end period: 2 = “Between first and second IMP administration”, 3 = “After second IMP administration” and 4 = “Ongoing at the end of the study”.

Subject’s concomitant medications will be coded using the WHO Drug dictionary version B3 WHO DDE sept 2017. The number and percentage of subjects who took concomitant medications ended on or after the first administration of contrast agent will be summarized according to ATC1.

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

The table and the listing that will be displayed are detailed in Sections 6.1.3.4.3 and 6.2.4 respectively.

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7. SHELLS FOR TABLES, FIGURES AND LISTINGS

All outputs will be produced using SAS® version 9.2.

All recorded data will be listed following the table order and structure of the eCRF. In addition, all derived data used in the analyses will be listed. The listings will include all subjects and will be ordered by site and subject.

Unless otherwise indicated, in case of continuous or ordinal variables summary statistics are the n, mean, SD, median, minimum and maximum. The mean and median will be reported to 1 decimal more than the data; SD to 2 more decimals than the data; and minimum and maximum to the same number of decimals as the data. In case of nominal variables, summary statistics are the n and the frequency in terms of percentage.

7.1. Contents of clinical study report section 14

See appendices.

7.2. Contents of clinical study report section 16.2

See appendices.

8. **REFERENCES**

1. Holm S et al. A Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics, 1979; 6: 65-70
2. ICH-E3 Note for Guidance on Structure and Content of Clinical Study Reports
3. Bland JM et al. Measuring agreement in method comparison studies. Statistical Methods in Medical Research, 1999; 8: 135-160
4. Barnhart HX et al. An Overview On Assessing Agreement With Continuous Measurement. Journal of Biopharmaceutical Statistics, 2007; 17: 529-569
5. Morgan CJ et al. Modeling lesion counts in multiple sclerosis when patients have been selected for baseline activity. Multiple Sclerosis 2010; 16: 926-934

9. **APPENDICES**

Contents of clinical study report section 14: see attached document “Guerbet - GDX-44-004 - SAP - Final1.0 - Attachment - Tables”.

Contents of clinical study report section 16.2: see attached document “Guerbet - GDX-44-004 - SAP - Final1.0 - Attachment - Listings”.