STATISTICAL ANALYSIS PLAN No GDX-44-016

Performance of Elucirem® (gadopiclenol) in Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) perfusion of brain

Phase IIIb clinical study

SPONSOR GUERBET B.P. 57400 95943 ROISSY CHARLES DE GAULLE CEDEX - FRANCE	**STATISTICAL ANALYSIS PLAN APPROVAL**
BIOSTATISTICIAN PPD PPD	**Date and Signature** Signed through eTMF Veeva vault
CLINICAL PROJECT MANAGER PPD PPD	**Date and Signature** Signed through eTMF Veeva vault

HISTORY FORM

Version	Date	Reason for change
V1.0	18 August 2023	
V2.0	06 May 2024	- Adding protocol deviations in Table 3 - Deleting duplicate protocol deviations in Table 3
V3.0	19 July 2024	- Removing of the interim analysis - Deleting of minor protocol deviations and grouping of protocol deviations in Table 3
V4.0	20 December 2024	- Rules added about lesion analysis (primary and secondary analysis) - Modification in TOC

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ARPS	All Randomized Patient Set
ARTPS	All Randomized and Treated Patient Set
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CBV	Cerebral Blood Volume
CI	Confidence Interval
CNS	Central Nervous System
CT	Computed Tomography
DSC	Dynamic Susceptibility Contrast
DRM	Data Review Meeting
EPI	Echo Planner Imaging
FAS	Full Analysis Set
FWHM	Full-Width at Half-Maximum
IBR	Independent Blinded Readers
ICF	Informed Consent Form
ICL	Imaging Core Laboratory
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NTEAE	Non-Treatment Emergent Adverse Event
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SPS	Screen Patient Set
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organisation

TABLE OF CONTENTS

HISTORY FORM **2**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **3**

1. SUMMARY OF THE STUDY PROTOCOL **6**

1.1. STUDY OBJECTIVES 6
1.1.1. Primary Objective *6*
1.1.2. Secondary Objectives *6*
1.2. STUDY DESIGN 6

2. EVALUATION CRITERIA **8**

2.1. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 8
2.1.1. Demographic data *8*
2.1.2. Study disease *8*
2.1.3. Medical history and concomitant diseases *8*
2.1.4. Imaging history related to contrast agent *8*
2.1.5. Prior medications and procedures *8*
2.1.6. Clinical laboratory *8*
2.1.7. MRI examination *9*
2.2. EFFICACY CRITERIA 9
2.2.1. Primary criterion *9*
2.2.2. Secondary efficacy Criteria *10*
2.3. SAFETY CRITERIA 10
2.3.1. Extent of Exposure *10*
2.3.2. Adverse Events *10*
2.3.3. Clinical laboratory evaluation *11*
2.3.4. Vital signs, physical findings and other observations related to safety *11*
2.3.5. Concomitant medications and procedures *11*

3. STATISTICAL METHODS **12**

3.1. GENERAL CONSIDERATIONS 12
3.2. NULL AND ALTERNATIVE HYPOTHESIS 12
3.3. DETERMINATION OF SAMPLE SIZE 13
3.4. ADJUSTMENT FOR COVARIATES 13
3.5. HANDLING OF DROPOUTS OR MISSING DATA 13
3.6. INTERIM ANALYSES AND DATA MONITORING 13
3.7. MULTICENTER STUDIES 13
3.8. MULTIPLE COMPARISONS/MULTIPLICITY 13
3.9. USE OF AN "EFFICACY SUBSET" OF SUBJECTS 13
3.10. ACTIVE CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE 14
3.11. EXAMINATIONS OF SUBGROUPS 14

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES **15**

5. STATISTICAL AND ANALYTICAL PLANS **16**

5.1. DISPOSITION OF SUBJECTS 16
5.2. DATA SETS ANALYSED AND PROTOCOL DEVIATIONS 16
5.3. MEASUREMENTS OF STUDY DRUG COMPLIANCE 21
5.3.1. Volume of the total bolus *21*
5.3.2. Volume of the preload bolus *22*

5.4. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 22
5.4.1. Demographic data *22*
5.4.2. Study disease *22*
5.4.3. Medical history and concomitant diseases *22*
5.4.4. Imaging history *22*
5.4.5. Prior medications and Procedures *22*
5.4.6. Clinical laboratory evaluation at baseline *23*
5.4.7. MRI examination *23*
5.4.8. Other baseline characteristics *23*
5.5. EFFICACY EVALUATION 23
5.5.1. Primary analysis *23*
5.5.2. Sensitivity analyses *24*
5.5.3. Supplementary analyses *24*
5.6. SAFETY EVALUATION 26
5.6.1. Extent of Exposure *26*
5.6.2. Adverse Events *26*
5.6.3. Clinical laboratory evaluation *28*
5.6.4. Vital signs, physical findings and other observations related to safety *29*
5.6.5. Concomitant medications and procedures *29*

6. LIST OF TABLES, FIGURES AND LISTINGS 29

6.1. CONTENTS OF CLINICAL STUDY REPORT SECTION 14 29
6.2. CONTENTS OF CLINICAL STUDY REPORT SECTION 16.2 33

7. REFERENCES 35

1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, Protocol No. GDX-44-016: "**Performance of Elucirem® (gadopiclenol) in Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) perfusion of brain**".

This analysis plan is based on the final protocol Version 1.0 dated September 30, 2022.

1.1. Study objectives

1.1.1. Primary Objective

To demonstrate the non-inferiority of DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg compared to DSC-MRI perfusion using Dotarem® at 0.1 mmol/kg in terms of diagnostic quality of Cerebral Blood Volume (CBV) perfusion map (off-site assessment).

1.1.2. Secondary Objectives

- To evaluate the diagnostic quality of CBV perfusion map for Elucirem® and Dotarem® (on-site assessment)
- To compare the performance of DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg to DSC-MRI using Dotarem® at 0.1 mmol/kg in differentiating glioma grade through the quantification of the relative CBV (rCBV, off-site assessment)
- To assess the reliability of the T2* signal intensity time curve in terms of confidence in diagnosis in DSC-MRI perfusion using Elucirem® at 0.05 mmol/kg (on-site and off-site assessments)
- To expand the previously established safety profile of Elucirem® at 0.05 mmol/kg in terms of incidence of adverse events (AEs).

1.2. Study design

The trial is designed as a prospective, multi-center, randomized, controlled and parallel arm comparison.

Once informed consent form (ICF) signed, the patients will perform a screening visit (V1) to confirm trial eligibility. The eligible patients will be randomized by Interactive Web Response System (IWRS) to determine the Investigational Medicinal Product (IMP) to be injected. They will undergo a DSC-MRI perfusion using Elucirem® or Dotarem® (MRI visit - V2).

A safety visit (V3) will be performed 1 day after the MRI visit by phone. Confirmation of tumor grade diagnosis, if available, will be collected up to 30 days after visit 2.

The randomization scheme will allocate patients in a 1:1 ratio to the two parallel arms. Stratification by glioma grades (low grades versus high grades) between the two arms will be managed by IWRS based on the diagnosis collected at screening.

Images will be evaluated by both on-site and off-site readers.

For on-site reads, at least one experienced neuroradiologist will be appointed in each investigational site at the start of the trial to read perfusion images of patients included at the site.

For off-site reads, all images will be sent to an Imaging Core Laboratory (ICL) which will prepare the images for evaluation. The off-site images evaluation will be performed by two Independent Blinded Readers (IBR) experienced in perfusion MRI and brain tumors. In case of discordance (for number of lesions detected, localization of the lesion(s), diagnostic quality of the CBV map (primary criterion), rCBV quantification (only the glioma grade, not the rCBV value) and/or visual evaluation of the T2* signal intensity time curve, including the confidence in the diagnosis), a consensus meeting will be organised in order to reach an

agreement. Matching of the lesion(s) assessed by the IBR, with the histopathological data provided by the site, if any, will be performed by a third reader (see Imaging Charter V1.0).

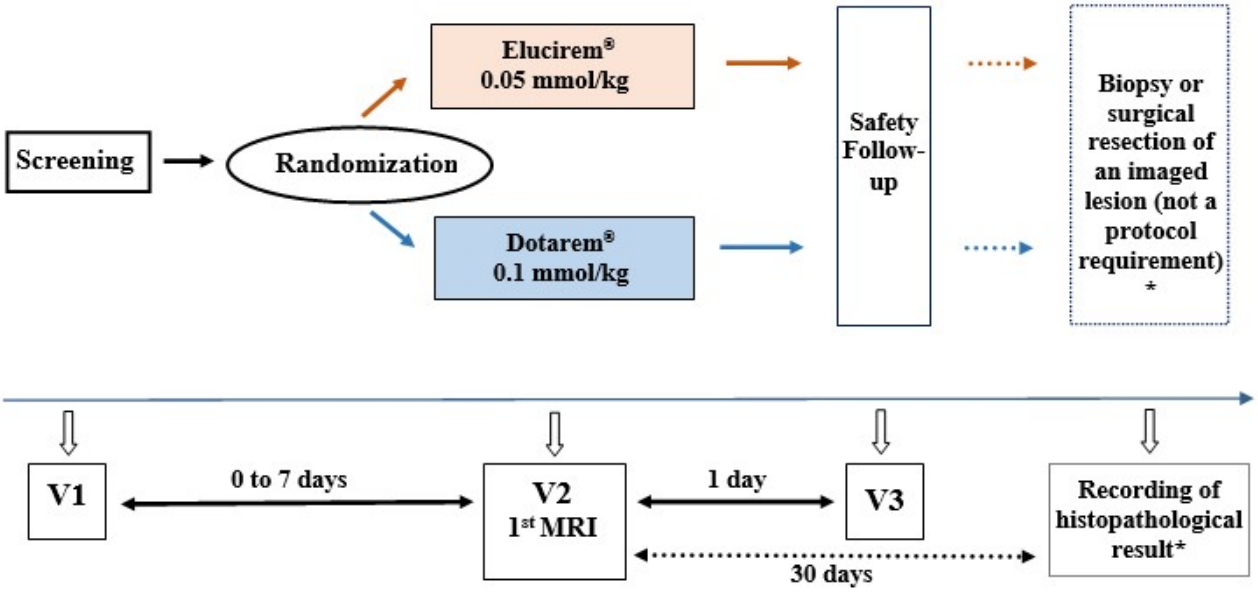
For this study, only off-site readers will be blinded to the nature of the Investigational Medicinal Product (IMP) injected.

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

During the trial, the safety of the patients will be monitored and assessed based on the reporting of AEs.

This trial will be an international trial conducted in several European countries.

The trial diagram is the following:



V: visit

Applicable to patients who undergo a biopsy or a surgery within 30 days after the MRI examination

Minimum trial duration for patients is 2 days, if V1 and V2 are done on the same day. Maximum trial duration for patients is 9 days if the screening period lasts 7 days.

Maximum trial duration for collection of data is 37 days if the screening period lasts 7 days and a biopsy or surgery is done 30 days after the MRI.

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

2.1.1. Demographic data

Demographic parameters are age (in years), categorized age (<65 and ≥65 years), sex, body weight (in kg (see section §3.1 for rule rounding), measured at V2), women of childbearing potential, result of the urinary pregnancy test for women with childbearing potential (performed at V1 and V2 if V2 performed more than one day after V1), women of childbearing potential (if not, the reason why), ethnic origin, and race.

2.1.2. Study disease

Baseline characteristics are the most recent type of image procedure to detect the glioma (CT, MRI, Other), primary glial tumor type (naive, recurrent), tumour localisation, grade of the primary glial tumor (low grade, high grade) according to the IWRS data and e-CRF.

Time between imaging procedure documenting the study disease and informed consent signature will be calculated in months as follow: (Informed consent signature date - procedure date in days) / 30.4375.

Time between imaging procedure documenting the study disease and injection of IMP will be calculated in months as follow: (study contrast agent administration date - procedure date in days) / 30.4375.

2.1.3. Medical history and concomitant diseases

Patient's medical history and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version in force at the time of database lock and tabulated by System Organ Class (SOC), Preferred Term (PT) and status. Medical histories are the ones flagged as "Not Ongoing" and concomitant diseases are those flagged as "Ongoing" at the screening visit.

2.1.4. Imaging history related to contrast agent

Imaging history related to contrast agent (≤ 5 or > 5 examinations) will be depicted by previous exposure to gadolinium complex, number of examination(s) and occurrence of AE.

2.1.5. Prior medications and procedures

Prior medications and procedures / therapeutic measures are defined as medications and procedures ended before the first administration of IMPs. Prior medications and procedures / therapeutic measures will be coded using the Anatomical Therapeutic Chemical (ATC) World Health Organisation (WHO) Drug dictionary and MedDRA latest version in force at the time of data base lock, respectively.

2.1.6. Clinical laboratory

Serum creatinine and eGFR will be measured at V1, Serum creatinine will be collected, in the e-CRF, either in mg/dL, µmol/L or mg/L.

The standard international units (SI) and conventional United States units (US) for these two parameters are listed below:

Table 1: Units for creatinine and eGFR

Biochemical parameters	Conventional Units	SI Units
Creatinine	mg/dL	µmol/L
eGFR	mL/min/1.73m²	mL/min/1.73m²

2.1.7. MRI examination

MRI examination parameters are:

- manufacturer of the MRI machine,
- magnetic field strength (in Tesla),
- Pre-injection Axial 3D T1 weighted GRE sequence performed,
- Pre-injection Axial 2D T2 weighted T(F)SE sequence performed,
- Pre-injection Axial 2D Flair sequence performed,
- Post-injection Axial DSC T2* perfusion sequence performed,
- Post-injection Axial 3D T1 weighted GRE sequence performed.

2.2. Efficacy criteria

CBV map is generated through a post-processing software for each DSC-MRI perfusion. Technical adequacy of perfusion CBV map is determined, by on-site and off-site readers (two readers blinded to the IMP), using a 4-point scale with the following grades:

- non-diagnostic,
- poor,
- fair,
- good.

CBV maps are considered technically non diagnostic if artifacts completely compromise image interpretability. Therefore, the assessment of primary and secondary criteria stops at this step.

The major artifacts are recorded as follows:

- Movement artifacts,
- T2* artifacts,
- Echo Planner Imaging (EPI) distortion,
- Other, to be specified.

Only for images considered technically adequate (i.e., poor, fair or good), the evaluation of primary and secondary criteria is performed.

2.2.1. Primary criterion

The primary criterion of the trial is the diagnostic quality of CBV map generated assessed **by off-site readers**. The following 4-point scale is used to assess the diagnostic quality of CBV map generated:

- 1: Poor: IC; EC; BG not distinguishable & CGM; SCWM; DWM not distinguishable
- 2: Fair: IC; EC; BG partially distinguishable on AS & CGM; SCWM; DWM partially distinguishable on 2S
- 3: Good: IC; EC; BG well distinguishable on 2S & CGM; SCWM; DWM well distinguishable on 2S
- 4: Excellent: IC; EC; BG well distinguishable on AS & CGM; SCWM; DWM well distinguishable on AS

with: IC=Internal Capsule; EC=External Capsule; BG=Basal Ganglia; CGM=Cortical Normal Appearing Gray Matter; SCWM=Sub-Cortical Normal Appearing White Matter; DWM=Deep Normal Appearing White Matter; AS=all slices; 2S=not more than 2 slices.

2.2.2. Secondary efficacy Criteria

On-site Evaluation of CBV Map Diagnostic Quality

The same 4-point scale, described in §2.2.1, is used to assess the diagnostic quality of CBV map generated by the **on-site readers**.

Quantification of the relative CBV for differentiating tumor grade (off-site assessment)

For each DSC-MRI perfusion, the rCBV will be calculated on the CBV perfusion map. The regions of interest (ROIs) will be placed by off-site readers on the tumors (i.e. lesions) for providing tumor CBV and on normal tissue (contralateral normal-appearing white matter) for providing referenced CBV.

Localization and size of the tumors assessed by the off-site readers will be compared to the targeted tumor concerned by the standard of truth for grading gliomas in order to check if there is a correspondence between SOT tumor and one of the tumors assessed by the off-site readers. Standard of truth will be the histopathological results collected on site (diagnosis based on the 2021 WHO classification of CNS tumors).

Assessment and evaluation of the T2* signal intensity time curve (on-site and off-site assessment)

T2* signal intensity time curve will be visually assessed by on-site and off-site readers for the reliability of the curve in providing sufficient information for diagnosis purpose. If the curve is assessed as reliable, the full-width at half-maximum (FWHM) and the maximum signal drop will be measured by off-site readers only.

Readers will record their confidence in diagnosis based on the reliability of the curve using a 5-point scale:

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

The rCBV, T2* signal intensity, FWHM and maximum signal drop will be assessed at lesion level. Analyses relative to rCBV will be performed at patient or patient / reader level and analyses relative to T2* signal intensity, FWHM and maximum signal drop will be performed at lesion or lesion / reader level. Of note, analyses for on-site reader at patient level are equivalent to lesion level as only one lesion is considered.

2.3. Safety criteria

2.3.1. Extent of Exposure

IMP (Elucirem® or Dotarem®) will be injected intravenously at the appropriate dose (0.05 mmol/kg or 0.1 mmol/kg, respectively) using a power injector with a minimum flow rate of 4 mL/second. This will be followed by a 20 mL bolus of 0.9% saline delivered at the same flow rate.

Preload bolus is allowed. If applied, the total dose (preload bolus + main bolus) of IMP (Elucirem® or Dotarem®) should not exceed 0.05 mmol/kg or 0.1 mmol/kg, respectively.

The following information will be recorded in the eCRF: date and time of IMP injection, actual volume administered, actual injection rate, brand of power injector used, overdose (if any), injection of saline flush (yes/no), volume of saline flush, event at injection site (yes/no), preload bolus (yes/no), and, if yes, the volume of preload bolus administered.

2.3.2. Adverse Events

AEs will be recorded throughout patient's participation. AEs will be coded using the last version of MedDRA dictionary at the time of the database lock.

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

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

An Adverse Event of Special Interest (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 this AESI.

AEs emergence will be defined as follows:

- Non-treatment emergent AE (NTEAE): if the AE starts prior to the IMP administration or if the patient is not injected.
- Treatment emergent AE (TEAE): if the AE starts on the date and time or after the IMP administration.

TEAEs with causal relationship to the IMP are those described by the investigator with causal relationship to the IMP equals to "related" or missing relationship.

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 IMP administration (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 IMP administration (i.e., year or year & month is/are the same as or after those of the date injection) then the AE is emergent.

Time to onset of AE will be calculated as follow: datetime of AE onset – datetime of IMP administration. If the AE start date is missing or unknown, it will be imputed as the treatment administration date.

When the start date of an AE is only partially known, it will be imputed so that the time to onset is minimal.

2.3.3. Clinical laboratory evaluation

Not Applicable.

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

Not Applicable.

2.3.5. Concomitant medications and procedures

Patient's concomitant medications will be coded using the ATC WHO Drug dictionary latest version in force at the date of database lock.

Patient's concomitant procedures will be coded using the MedDRA dictionary latest version in force at the date of the database lock.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed by a CRO 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 arm. Summary tabulated results will be provided by arm 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 Patients / Mean / Standard Deviation (SD) / Minimum / Median / 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.

Rules for rounding decimals (example= the weight):
If decimal is <0.5 then round the number down (example: 65.3kg is rounded to 65kg)
If decimal is ≥0.5 then round the number up (example: 65.6kg is rounded to 66kg)

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 arm. Percentages will be rounded to one decimal place.

The baseline value will be defined as the last available value prior to administration of the investigational product.

All statistical tests will be performed at the significant threshold of 2.5% one sided (5% two-sided).

SAS® Version 9.4 (or later version) will be used for all descriptive summaries and inferential analyses.

3.2. Null and alternative hypothesis

Statistical hypotheses

From a clinical perspective, a 12% non-inferiority margin was not considered importantly different on diagnostic quality of contrast agents, therefore it is relevant to establish acceptable diagnostic quality of Elucirem® relative to Dotarem®.

The statistical hypotheses are the followings:

- H0: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} \leq -0.12$

- H1: $p_{(\text{excellent+good for Elucirem®})} - p_{(\text{excellent+good for Dotarem®})} > -0.12$

Non-inferiority will be evaluated by testing whether the lower bound of the two-sided Confidence Interval (CI) for the difference of "Elucirem®– Dotarem®", in proportion of patients presenting with images of excellent and good diagnostic quality according to off-site readers, excludes a 12% difference.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority (lower bound of the CI is above 0).. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

3.3. Determination of sample size

Sample sizes of 62 in each arm achieve 80% power to detect a difference of 0 when the non-inferiority difference is -0.12. In the reference arm (Dotarem®), the proportion of patients presenting with CBV map of excellent and good diagnostic quality is 94% [1]. In the Elucirem® arm, this proportion is assumed to be 82% under the null hypothesis. The power was computed for the case when the actual treatment arm proportion is 94%. The statistical test used is the one-sided Z test (unpooled). The significance level of the test is 2.5% (unilateral, 5% bilateral).

Assuming a 10% drop-out rate, the sample size increases to 138 patients to test that the proportion of patients presenting with images of excellent and good quality in the Elucirem® arm is not inferior to the proportion of patients presenting with images of excellent and good quality in the Dotarem® arm.

The sample size was calculated using the PASS statistical software by Exystat.

3.4. Adjustment for covariates

Not Applicable.

3.5. Handling of dropouts or missing data

Not Applicable.

3.6. Interim analyses and data monitoring

No interim analysis is planned.

3.7. Multicenter studies

As the primary criterion is evaluated by off-site-readers, the site effect will not be included in the primary analyses.

3.8. Multiple comparisons/Multiplicity

Multiple testing regarding secondary criteria (quantification of rCBV) will be taken into account by using the Benjamini-Hochberg method.

The adjusted p-values according to the Benjamini-Hochberg procedure will be calculated as follows:

$$p\ \text{Benjamini-Hochberg} = \min(p \times nbp / j, 1)$$

where:

- p is the original p-value (without adjustment),
- nbp is the number of calculated p-values (i.e., the number of comparisons),
- j is the rank of the original p-value when all p-values are ranked in ascending order.

3.9. Use of an “efficacy subset” of subjects

As the primary objective is to demonstrate non-inferiority of Elucirem® compared to Dotarem®, the corresponding analysis will be done using the PPS and then will be repeated using the FAS.

3.10. Active control studies intended to show equivalence

Not Applicable.

3.11. Examinations of subgroups

Not Applicable.

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

An interim analysis (IA) on the primary evaluation criterion was planned to be performed when 50% of the patients are assessed by the off-site readers, in terms of diagnostic quality of images.
Based on this analysis, an internal committee had the possibility to decide to early terminate the trial if the lower bound of the two-sided 99.8% CI was above the pre-stated margin of noninferiority (-12%) as Elucirem® would be declared non-inferior to Dotarem® for efficacy.

Due to unanticipated concomitance of recruitment pace and biometry operations, the result of the IA would have been available only when all patients would have been included and treated and so would not have had any impact on the recruitment and the study. Therefore, it was decided to not perform the IA in June 2024.

As only one analysis is done, there is no need to adjust the Type I error. Therefore, the final analysis will be performed at a significant level of 0.025 (unilateral, 0.05 bilateral) leading to the construction of a two-sided 95% CI for the non-inferiority testing.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of subjects

Patient disposition will be based on all patients who have signed their ICF and tabulated, by arm and overall for the following categories:

- Number (percentage) of patients in each Data Set,
- Number (percentage) of patients overall disposition,
- Number (percentage) of patients by trial visit,
- Number (percentage) of patients by country and center,
- Number (percentage) of patients screen failed (only overall) and prematurely discontinued from the trial,
- Reason for screen failure (only overall) and premature discontinuation.

5.2. Data Sets Analysed and protocol deviations

Data sets analysed

The patient sets for this trial, will be presented by arm and overall, and are defined below:

- Screened Patients Set (SPS) will include all patients having signed the ICF,
- All Randomized Patients Set (ARPS) will include all patients having signed the inform consent form and randomized according to the assigned treatment arm,
- All Randomized and Treated Patients Set (ARTPS) will include all patients having signed the inform consent form, randomized according to the assigned treatment arm and treated in the trial,
- Full Analysis Set (FAS) will include all patients who have a valid primary criterion assessment, that is to say images available, with a perfusion CBV map considered as technically adequate (i.e., poor fair, good) and read. Patients will be analysed according to the treatment arm assigned at randomization. Two FAS will be considered in this study:
    - Off-site FAS taking into account off-site assessments for the two off-site readers,
    - On-site FAS: taking into account on-site assessments.
- Per-Protocol Set (PPS) will include all patients from the FAS who have no major protocol deviations and who have complied with the treatment allocated at randomization. Two PPS will be considered in this study:
    - Off-site PPS: all patients from the Off-site FAS and without major protocol deviations for both assessments and specific to the off-site assessment,
    - On-site PPS: all patients from the On-site FAS and without major protocol deviations for both assessments and specific to the on-site assessment,
- Safety Set (SS) will include all patients having received at least one injection of IMP regardless of the quantity. Patients will be analysed according to the treatment really received.

Table 2: Datasets analysed

	Screened Patient Set (SPS)	Safety Set (SS)	Full Analysis Set (FAS)		Per Protocol Set (PPS)	
			Off-site FAS	On-site FAS	Off-site PPS	On-site PPS
Disposition	✓					
Protocol Deviation	✓					
Population characteristics at baseline			✓		✓	
Exposure		✓				
Efficacy: Primary criterion			✓		✓	
Efficacy: Secondary criteria			✓	✓	✓	✓
Safety		✓				
Data Listings	✓					

Protocol deviations

As per 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, before locking the database. Protocol deviations will be gathered from monitoring files, clinical database, IWRS database and external vendors of off-site data (Imaging).

Protocol deviations will be categorized into major and non-major deviations. A major deviation is defined as a deviation having **an impact on the primary criterion** (diagnostic quality of the CBV map generated according to off-site readers) and an impact on the secondary criterion regarding the diagnostic quality of the CBV map generated according to on-site readers. A first categorisation is done in this document, then categorisation will be reviewed before database lock, during the statistical Data Review Meeting (DRM). The decision will be duly described in the meeting minutes.

The deviations are listed in the table below:

Table 3: Listing of protocol deviations

Categorisation of the deviation	Protocol Deviation Coded Term	Source	Status
Inclusion criteria not met	Patient having not reached legal majority age	Clinical Database	Non major for both assessments
	Patient not presenting, at the time of inclusion, naïve or recurrent primary glial tumor and/or tumor grade are not available in patients' medical records	Clinical Database	Major for both assessments
	Patient having not signed the ICF	Clinical Database	Major for both assessments

Categorisation of the deviation	Protocol Deviation Coded Term	Source	Status
	Patient not affiliated to national health insurance according to local regulatory requirements	Clinical Database	Non major for both assessments
Non-inclusion criteria met	Patient with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to other GBCAs (such as hypersensitivity, post-contrast acute kidney injury)	Clinical Database	Non major for both assessments
	Patient presenting with any contraindication to MRI examinations	Clinical Database	Non major for both assessments
	Post treatment patient presenting with pseudo-progression instead of tumor recurrency	Clinical Database	Major for both assessments
	Patient presenting with severe renal insufficiency, defined as an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m^2 assessed within 1 day prior to contrast agent injection	Clinical Database	Non major for both assessments
	Patient having received any contrast agent (MRI or CT) within 3 days prior to IMPs administration or scheduled to receive any contrast agent within 24 hours after IMP administration	Clinical Database and monitoring	Major for both assessments for the first part of the criterium Non major for both assessments for the second part of the criterium
	Pregnant female patient (a female patient of childbearing potential or with amenorrhea for less than 12 months must have a negative pregnancy test within 1 day prior to trial MRI and must be using medically approved contraception method until the last trial visit)	Clinical Database	Non major for both assessments
	Patient having received any investigational medicinal product within 7 days prior to trial entry or scheduled to	Clinical Database	Non major for both assessments

Categorisation of the deviation	Protocol Deviation Coded Term	Source	Status
	receive any investigational treatment in the course of the trial		
	Patient previously randomized in this trial	Clinical Database	Major for both assessments
	Patient with anticipated, current or past condition (medical, psychological, social or geographical) that would compromise the patient's safety or her/his ability to participate in the trial	Clinical Database	Non major for both assessments
	Patient unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits and/or unlikelihood of completing the trial	Clinical Database	Non major for both assessments
	Patient related to the investigator or any other trial staff or relative directly involved in the trial conduct	Clinical Database	Non major for both assessments
Imaging	Imaging acquisitions guidelines not respected with major impact on the primary criterion / Image technically not adequate at V2 according to off-site reader	Imaging QC (external vendors off site data)	Major for Off-site assessment
	Imaging acquisitions guidelines not respected with non-major impact on the primary criterion or on secondary criteria	Imaging QC (external vendors off site data)	Non major for Off-site assessment
Forbidden concomitant medication	Any contrast agent (MRI or CT) administered during the course of the trial or within 24 hours after the trial product administration	Clinical Database	Non major for both assessments
IMP deviation	Patient does not receive the IMP allocated by randomization on the IRT system and IMP is different from the one allocated	IWRS Database	Major for both assessments
	Patient does not receive the IMP allocated by	IWRS Database	Non major for both assessments

Categorisation of the deviation	Protocol Deviation Coded Term	Source	Status
	randomization on the IRT system and IMP received is the same from the one allocated		
	The IMPs volume actually administered is different from the theoretical one from 5 to 10 % (relative difference)	Clinical database, IWRS database	Non major for both assessments
	The IMPs volume actually administered is different from the theoretical one by more than 10 % (relative difference)	Clinical database, IWRS database	Major for both assessments
	Injection rate <4 mL/sec	Clinical database	Major for both assessments
	The volume of saline flush injected is different from 20 mL	Clinical database	Non major for both assessments
	Temperature excursion for IMP	Monitoring	Non major for both assessments
	IMP management not appropriate	Monitoring	Non major for both assessments
Missing data	Blood sampling for Serum creatinine result and EGFR calculation is not performed at screening	Clinical Database	Non major for both assessments
	Pre-injection Axial 3D T1 weighted GRE sequence performed is not performed	Clinical Database	Non major for both assessments
	Pre-injection Axial 2D T2 weighted T(F)SE sequence performed is not performed	Clinical Database	Non major for both assessments
	Pre-injection Axial 2D Flair sequence performed is not performed	Clinical Database	Non major for both assessments
	Post-injection Axial DSC T2* perfusion sequence is not performed	Clinical Database	Major for both assessments
	Post-injection Axial 3D T1 weighted GRE sequence is not performed	Clinical Database	Non major for both assessments
Non respect of study's schedule and procedures	Grade collected at randomization is not the same as the grade collected in the e-CRF	Clinical database, IWRS database	Major for both assessments

Categorisation of the deviation	Protocol Deviation Coded Term	Source	Status
	For women of childbearing potential, pregnancy test positive or not performed within 1 day before IMP administered	Clinical Database	Non major for both assessments
	eGFR assessment performed more than 7 days before the IMP administration	Clinical Database	Non major for both assessments
	The patient complete the study and the Safety visit (V3) is not performed	Clinical Database	Non major for both assessments
	Safety visit (V3) performed more than 1 day compared to V2	Clinical Database	Non major for both assessments
GCP deviation	Deviations related to ICF management process	Monitoring	Non major for both assessments
	Source document management not appropriate	Monitoring	Non major for both assessments
	SAE management not appropriate	Monitoring	Non major for both assessments
	Personal data breach	Monitoring	Non major for both assessments
	Other GCP deviations	Monitoring	Non major for both assessments

Patients presenting at least one protocol deviation with a status major will be excluded from the PPS (Off-site PPS and / or On-site PPS).

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 and major protocol deviations will be flagged.

5.3. Measurements of study drug compliance

Drug compliance will be presented using the off-site PPS.

5.3.1. Volume of the total bolus

The number of patients with actual total volume of IMPs equal and different (less or greater) from the theoretical one will also be presented by arm.

Moreover, the absolute (mL) and relative (%) differences between theoretical and actual volumes of IMPs will be presented quantitatively and qualitatively (in classes) by arm.

Theoretical volume will be calculated by multiplying the body weight measured at the V2 by 0.1 mL for Elucirem and 0.2 mL for Dotarem and rounded to the nearest integer.

The absolute difference will be calculated as follow: actual volume – theoretical volume.

The relative difference will be calculated as follow: abs (actual volume – theoretical volume) / theoretical volume.

5.3.2. Volume of the preload bolus

The number of patients with a preload bolus will be tabulated by arm.

Listing of measurements of compliance with trial drug will be presented in CSR appendix 16.2.5.

5.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics (except clinical laboratory data) will be presented on the Off-site PPS and on the Off-site FAS. Clinical laboratory data will be presented on the Off-site PPS and on the SS.

5.4.1. Demographic data

Demographic parameters will be described per arm and overall, with descriptive statistics.

Listing of demographic data will be presented in CSR Appendix 16.2.4.

5.4.2. Study disease

The study disease and its characteristics (type, grade according to IWRS and e-CRF), the localisation of the tumour, the procedure documenting the study disease, the time between imaging procedure and first injection of IMPs (in months) and the time between imaging procedure and informed consent signature (in months) will be presented by arm and overall with descriptive statistics.

Listing related to study disease will be presented in CSR Appendix 16.2.4.

5.4.3. Medical history and concomitant diseases

Summary tables (number and % of patients) grouped by SOC and PT will be presented by arm and overall for medical history firstly then for concomitant diseases.

Tables will be sorted by descending frequency of SOC and, within each SOC, by descending frequency of PT according to the overall column.

The number and percentage of patients presenting with at least one Medical History under medication will be presented.

Listing of all diseases, with a flag for ongoing diseases will be presented in CSR Appendix 16.2.4.

5.4.4. Imaging history

Summary tables (number and % of patients) will be presented by arm and overall for previous exposure to gadolinium complex, number of examination(s) and occurrence of AE.

5.4.5. Prior medications and Procedures

Summary tables (number and % of patients) grouped by ATC codes (Version WHO Drug September 2024) will be presented for prior medications (those with “End of Treatment” coded 1) and by SOC and PT for prior procedures (those with “End Date” of the procedure inferior to the date of the IMPs administration).

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

Listing of all medications and procedures will be presented in CSR Appendix 16.2.4.

5.4.6. Clinical laboratory evaluation at baseline

Serum creatinine and eGFR data will be presented by arm using the Off-site PPS, Off-site FAS and SS. Time between blood drawing at V1 and MRI performed at V2 will be calculated as follow: (MRI date - blood drawing date in days).

Serum creatinine and eGFR data will be analysed quantitatively. eGFR will be also analysed qualitatively.

Quantitative analyses will be performed by tabulating the raw data.

Qualitative analysis of eGFR will present number of patients with value:

- <30 mL/min/1.73m2,
- ≥30 and <60 mL/min/1.73m2,
- ≥60 and <90 mL/min/1.73m2,
- ≥90 mL/min/1.73m2.

Listing of all laboratory evaluation at baseline will be presented in CSR Appendix 16.2.8.

5.4.7. MRI examination

All the sequences performed during the MRI examination as well as the magnetic field strength (in Tesla) will be tabulated by arm.

Listing of MRI examinations will be presented in CSR Appendix 16.2.4.

5.4.8. Other baseline characteristics

For women with childbearing potential, summary table (number and % of patients) of the test performed or not and the result of the test will be displayed (positive, negative), at V1 and V2 (if V2 performed more than one day after V1), by arm and overall.

Listing of all other baseline characteristics will be presented in CSR Appendix 16.2.4.

5.5. Efficacy evaluation

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

5.5.1. Primary analysis

The primary endpoint of the trial is the proportion of patients presenting with CBV map of excellent and good diagnostic quality, according to off-site readers, in the Elucirem® and the Dotarem® arm.

Technical adequacy of perfusion CBV map will be tabulated on the ARTPS, Off-site PPS and Off-site FAS, for each off-site reader, according to the following scale:

- non-diagnostic,
- poor,
- fair,
- good.

Of note, patients for whom the technical adequacy of perfusion CBV map will be assessed as "non-diagnostic", by at least one off-site reader, will be excluded from the Off-site FAS and Off-site PPS.

For the perfusion CBV map that will be evaluated by the off-site readers, as technically non-diagnostic (artifacts that completely compromise the image interpretability), the major artifacts will be tabulated and presented for each off-site reader on the ARTPS:

- Movement artifacts,

- T2* artifacts (any non-evaluable series like black series due to susceptibility issues linked to magnetic issues),
- EPI distortion,
- Other.

Non-inferiority will be assessed by calculating the difference in proportion of patients presenting with images of excellent and good diagnostic quality, after consensus between off-site readers, between Elucirem® and Dotarem® arms, and by constructing a two-sided 95% CI around this difference. If the lower bound of the two-sided 95% CI is above the pre-stated margin of non-inferiority (-12%), Elucirem® will be declared non-inferior to Dotarem®.

The Wald statistical test with a continuity correction will be used.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority (lower bound of the CI is above 0). No adjustment for multiplicity is needed as it is a simple closed testing procedure.

The primary analysis will be performed on the Off-site PPS and then on the Off-site FAS and presented by arm only on one hand, and by arm and grade assigned at randomization on the other hand.

5.5.2. Sensitivity analyses

Not Applicable.

5.5.3. Supplementary analyses

Intra-reader variability at patient level

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

For the primary evaluation criterion, intra-reader variability will be studied using the Cohen kappa (κ) statistics. Agreement will be classified according to the value of the Cohen kappa statistics as described in the table below:

Table 4: Agreement according to Cohen kappa (κ) statistics

Cohen kappa statistics	Agreement
< 0.2	Poor agreement
≥ 0.2 –≤ 0.4	Fair agreement
> 0.4 –≤ 0.6	Moderate agreement
> 0.6 –≤ 0.8	Good agreement
> 0.8 – 1.0	Very good agreement

Inter-reader variability at patient level

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

The same methodology as the one presented above for intra-reader variability will be applied.

Diagnostic quality of CBV map assessed by on-site readers

The same methodology and analyses as the ones presented for the primary criterion will be applied to diagnostic quality of the CBV map according to the on-site readers.

If the primary endpoint concluded to the non-inferiority of Elucirem versus Dotarem (off-site readers), then the non-inferiority will be tested for on-site readers: If the lower bound of the two-sided 95% CI is above the pre-stated margin of non-inferiority (-12%), Elucirem® will be declared non-inferior to Dotarem®.

In case of conclusion of non-inferiority of Elucirem® compared to Dotarem®, the superiority of Elucirem® compared to Dotarem® will then be tested in the same way as described above for the non-inferiority. No adjustment for multiplicity is needed as it is a simple closed testing procedure.

This secondary analysis will be performed on the On-site PPS and then on the On-site FAS and presented by arm only on one hand, and by arm and grade assigned at randomization on the other hand.

Quantification of the relative CBV for differentiating tumor grade (off-site assessment)

The Mann-Whitney U-test will be used to test the difference in rCBV between the two trial arms by tumor grade categorization (low and high grade) and between patients with high-grade and low-grade gliomas, within each of the two study arms at the significant level of 5%. The analysis will be performed for off-site assessment and presented for each off-site reader and overall (taking into account the consensus decision).

If more than one lesion were detected by a reader, the maximum value for rCBV will be considered for the analysis at reader level. For the overall rCBV analysis taking into account the consensus decision, the maximum value for rCBV of consensus reading will be considered. If no consensus was needed, the maximum value for rCBV between the two off-site readers will be considered.

Two analyses will be performed. The first one will consider the gliomas' grade categorization (high-grade versus low-grade) according to the stratification factor used at randomization, the second one will use the tumor grade categorization as per histopathological results (if any) collected during the study.

Categorization as per histopathological results will be the following:

- Grade 1 and Grade 2 = Low grade,
- Grade 3 and Grade 4 = High grade.

The Benjamini-Hochberg method will be used to account for multiple testing for the two analyses separately.

Grade per categorization (high-grade versus low-grade) according to the stratification factor used at randomization will be cross tabulated with the categorization of the grade as per off-site reader assessment, by treatment arm.

If more than one lesion were detected by a reader, the worst grade according to rCBV will be considered. Then, for the overall analysis of grade according to rCBV taking into account the consensus decision, the worst grade according to rCBV of consensus reading will be considered. If no consensus was needed, the worst grade according to rCBV between the two off-site readers will be considered. Moreover, for patients with histopathological results, categorization of the grade per histopathology will be cross tabulated with the categorization of the grade as per off-site reader assessment, by treatment arm.

Categorization as per off-site reader assessment will be the following (according to the Imaging Charter V1.0):

- rCBV < 1.75 = Low grade,
- rCBV ≥ 1.75 = High grade.

Assessment and evaluation of the T2* signal intensity time curve at lesion level (on-site and off-site assessment)

T2* signal intensity time curve will be visually assessed by on-site and off-site readers for the reliability of the curve in providing sufficient information for diagnosis purpose.

For on-site assessment, the number and percentage of lesions for whom the reliability of the curve provides suffice information will be tabulated by trial arms.

For the off-site assessment, the number and percentage of lesions for whom the reliability of the curve provides suffice information will be tabulated by trial arms.

For lesions for whom the reliability of the curve provides suffice information, confidence in diagnosis will be presented, for each arm, by on-site readers and for the off-site assessment for each off-site reader, using a 5-point scale:

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

Confidence in diagnosis will be summarized qualitatively and quantitatively by trial arm. The on-site and off-site read outcomes will be separately analyzed.

For the overall reliability of the T2* signal intensity time curve taking into account the consensus decision, the worst confidence in diagnosis between the two readers will be considered if no consensus decision was needed (worst case scenario).

Assessment and evaluation of the T2* signal intensity time curve (off-site assessment)

Only for off-site readers, FWHM and the maximum signal drop will be tabulated at lesion level by off-site reader and compared between the trial arms using a Mann-Whitney U-test.

For the overall FWHM taking into account the consensus decision, the mean of values between the two readers for each lesion will be considered if no consensus decision was needed.

For the overall maximum signal drop taking into account the consensus decision, the maximum of values between the two readers for each lesion will be considered if no consensus decision was needed.

If the curve is not reliable, no calculation of FWHM and the maximum signal drop will be performed.

5.6. Safety Evaluation

5.6.1. Extent of Exposure

The extent of exposure summary will be presented using the SS.

Duration (in days) between ICF signature and the IMPs administration, time from IMP administration to patient's last contact date, time from signature of ICF to patient's last contact date and time from MRI and histopathology will be tabulated by arm.

Descriptive statistics of the actual total volume (including the preload and main bolus) of IMPs will be presented by arm. Descriptive statistics of the actual volume of the preload bolus of IMPs will be presented by arm.

Occurrence of overdose (if any), actual injection rate of administration, brand of power injector used and volume of saline flush injected (if any) will be tabulated by arm.

Frequency tabulation of actual injection rate will be also displayed per arm according to following classes:

- ≥ 4 mL/s and ≤ 6 mL/s,
- > 6 mL/s.

Listing of extent of exposure and exposure will be presented in CSR appendix 16.2.1 and 16.2.7, respectively.

5.6.2. Adverse Events

NTEAEs

An overall summary of NTEAEs will be presented using the SPS. The table will be presented with the overall "Total" column only.

The total number of events and number of patients with at least one event will be tabulated for the following events:

- All NTEAEs,
- NTEAEs according to intensity (patients with AEs having different intensities will be counted in each category of intensity),
- NTEAEs according to the outcome (patients with AEs having different outcomes will be counted in each category of outcome),
- NTEAEs requiring an AE-targeted medication,
- NTEAEs requiring another AE-targeted action,
- NTEAEs leading to study discontinuation,
- Serious NTEAEs (variable "serious" classified as yes or missing) and by seriousness criteria (patients with AEs having different seriousness criteria will be counted in each category of seriousness criterion),
- AEs of special interest (AESIs) (preferred term is Nephrogenic systemic fibrosis).
- AEs with causal relationship to a study procedure.

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

The number and percentage of patients with at least one NTEAE and the number of NTEAE will be presented overall according to Primary SOC and PT.

TEAEs

The same overview will be displayed by arm for Treatment Emergent AEs (TEAEs) using the SS. The terms "NTEAE" will be replaced by "TEAE". The following variables will be presented in addition:

- TEAEs with causal relationship to the IMP.
- TEAEs leading to interruption of the IMP.

The number and percentage of patients with at least one TEAE and the number of TEAE will be presented by arm and overall according to Primary SOC and PT.

TEAEs with Causal Relationship to the IMP

The number and percentage of patients with at least one TEAE with causal relationship to the IMP and the number of corresponding TEAE will be presented by arm and overall 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 missing.

TEAEs with Causal Relationship to a Study Procedure

The number and percentage of patients with at least one TEAE with causal relationship to a study procedure and the number of corresponding TEAE will be presented by arm and overall 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".

TEAEs requiring an AE-targeted medication

The number and percentage of patients with at least one TEAE (whatever the causal relationship) requiring an AE-targeted medication and the number of corresponding TEAE will be presented by arm and overall according to Primary SOC and PT.

TEAEs requiring an AE-targeted therapeutic measure

The number and percentage of patients with at least one TEAE (whatever the causal relationship) requiring another AE-targeted action and the number of corresponding TEAE will be presented by arm and overall according to Primary SOC and PT.

TEAEs requiring an AE-targeted procedure

The number and percentage of patients with at least one TEAE (whatever the causal relationship) requiring another AE-targeted action and the number of corresponding TEAE will be presented by arm and overall according to Primary SOC and PT.

TEAEs requiring trial discontinuation

The number and percentage of patients with at least one TEAE (whatever the causal relationship) requiring trial discontinuation and the number of corresponding TEAE will be presented by arm and overall according to Primary SOC and PT.

TEAEs requiring IMPs interruption

The number and percentage of patients with at least one TEAE (whatever the causal relationship) requiring IMPs interruption and the number of corresponding TEAE will be presented by arm and overall according to Primary SOC and PT.

Serious TEAEs

The number and percentage of patients with at least one serious TEAE (whatever the causal relationship, related to IMPs and related to the study procedure itself) and the number of corresponding serious TEAE will be presented by arm and overall according to Primary SOC and PT.

Serious TEAEs with Causal Relationship to the IMP

The number and percentage of patients with at least one serious TEAE with causal relationship to the IMP and the number of corresponding serious TEAE will be presented by arm and overall according to Primary SOC and PT.

Serious TEAEs with Causal Relationship to a Study Procedure

The number and percentage of patients with at least one serious TEAE with causal relationship to a study procedure and the number of corresponding serious TEAE will be presented by arm and overall according to Primary SOC and PT.

Serious TEAEs leading to death

The number and percentage of patients with at least one serious TEAE (whatever the causal relationship) leading to death and the number of corresponding serious TEAE will be presented by arm and overall according to Primary SOC and PT.

AESI

The number and percentage of patients with at least one AESI (whatever the causal relationship) and the number of corresponding AESI will be presented by arm and overall according to Primary SOC and PT.

All tables will be sorted by descending frequency of SOC and, within each SOC by descending frequency of PT according to the overall column.

Deaths, serious adverse events and other significant adverse events

Deaths, SAEs and AESI will be listed (if any). These listings will be sorted by patient number, actual treatment arm, date/time of IMPs administration, date/time of onset of the AE, end date, Primary SOC, PT, and description.

Listing of adverse events will be presented in CSR appendix 16.2.7.

5.6.3. Clinical laboratory evaluation

Not Applicable

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

Not Applicable.

5.6.5. Concomitant medications and procedures

Concomitant medications will be coded using the latest WHO Drug dictionary version in force at the date of data base lock. Incidence of concomitant medications will be tabulated. The number and percent of patients taking concomitant medications will be presented. The denominator will be the number of patients in the SS.

Summary tables (number and % of patients) grouped by the first and the last level of ATC code will be presented whatever the purpose and when purpose is only for AEs (purpose coded 2), respectively. Concomitant medications are those ongoing ("Start Period" coded 2) after IMPs administration.

Listing of all concomitant medications will be presented in CSR appendix 16.2.4.

Concomitant procedures will be coded in System Organ Class (SOC) and Preferred term (PT) using the MedDRA version in force at the time of the Database lock. Incidence of concomitant procedures will be tabulated. The number and percent of patients undergoing concomitant procedures will be presented. The denominator will be the number of patients in the SS.

Summary tables (number and % of patients) grouped by SOC and PT will be presented when the "Start Date" of the procedure is superior or equal to the date of IMPs administration.

Listing of all concomitant medications and procedures will be presented in CSR appendix 16.2.4.

6. LIST OF TABLES, FIGURES AND LISTINGS

6.1. Contents of clinical study report section 14

14.1 DEMOGRAPHIC DATA

14.1.1 DISPOSITION OF PATIENTS
- Table 14.1.1.1 Number of Patients in Each Data Set – Screened Patient Set (SPS)
- Table 14.1.1.2 Patient Overall Disposition – Screened Patient Set (SPS)
- Table 14.1.1.3 Patient Disposition by Visit – Screened Patient Set (SPS)
- Table 14.1.1.4 Number of Patients by Center – Screened Patient Set (SPS)
- Table 14.1.1.5 Reasons for Screen-Failure – Screened Patient Set (SPS)
- Table 14.1.1.6 Reasons for Premature Discontinuation –All Randomized Patient Set (ARPS)

14.1.2 PROTOCOL DEVIATIONS
- Table 14.1.2.1 Protocol Deviations – Screened Patient Set (SPS)
- Table 14.1.2.2 Major Protocol Deviations – Screened Patient Set (SPS)
- Table 14.1.2.3 Non-major Protocol Deviations – Screened Patient Set (SPS)

14.1.3 DATA SETS ANALYSED

See Table 14.1.1.1.

14.1.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS
- Table 14.1.4.1 Demographic Characteristics at Screening Visit (V1) – Off-site FAS
- Table 14.1.4.2 Demographic Characteristics at Screening Visit (V1) –Off-site PPS
- Table 14.1.4.3 Study Disease – Diagnosis of The Glioma At Screening Visit (V1) –Off-site FAS
- Table 14.1.4.4 Study Disease – Diagnosis of The Glioma At Screening Visit (V1) –Off-site PPS
- Table 14.1.4.5 Grade of the primary glial tumor by treatment arm assigned at randomization and by grade (stratification variable at randomization) At Screening Visit (V1) –Off-site FAS
- Table 14.1.4.6 Grade of the primary glial tumor by treatment arm assigned at randomization and by grade (stratification variable at randomization) At Screening Visit (V1) –Off-site PPS

Table 14.1.4.7 Imaging History At Screening Visit (V1) –Off-site FAS
Table 14.1.4.8 Imaging History At Screening Visit (V1) –Off-site PPS
Table 14.1.4.9 Medical History At Screening Visit (V1) –Off-site FAS
Table 14.1.4.10 Medical History At Screening Visit (V1) –Off-site PPS
Table 14.1.4.11 Medical History Under Medication at Screening Visit (V1) –Off-site FAS
Table 14.1.4.12 Medical History Under Medications at Screening Visit (V1) –Off-site PPS
Table 14.1.4.13 Prior Medications According to ATC System Main Group –Off-site FAS
Table 14.1.4.14 Prior Medications According to ATC System Main Group –Off-site PPS
Table 14.1.4.15 Procedures Undergone Between Informed Consent Signature And Administration of IMPs By System Organ Class And Preferred Term –Off-site FAS
Table 14.1.4.16 Procedures Undergone Between Informed Consent Signature And Administration of IMPs By System Organ Class And Preferred Term –Off-site PPS
Table 14.1.4.17 Serum Creatinine Results And eGFR At Screening Visit (V1) - Off-site FAS
Table 14.1.4.18 Serum Creatinine Results And eGFR At Screening Visit (V1) –Off-site PPS
Table 14.1.4.19 Serum Creatinine Results And eGFR At Screening Visit (V1) - Safety Set (SS)
Table 14.1.4.20 MRI Examination At V2 - Off-site FAS
Table 14.1.4.21 MRI Examination At V2 –Off-site PPS
Table 14.1.4.22 Pregnancy Test At V1 - Off-site FAS
Table 14.1.4.23 Pregnancy Test At V1 – Off-site Per Protocol Set (Off-site PPS)
Table 14.1.4.24 Pregnancy Test At V2 (if V2 performed more than one day after V1) - Off-site FAS
Table 14.1.4.25 Pregnancy Test At V2 (if V2 performed more than one day after V1) –Off-site PPS

14.1.5 COMPLIANCE
Table 14.1.5.1 Total volume of IMP administered –Off-site PPS
Table 14.1.5.2 Preload Bolus administration –Off-site PPS

14.2 EFFICACY

14.2.1 PRIMARY ANALYSIS
Table 14.2.1.1 Technical adequacy of perfusion CBV map by off-site readers by treatment arm assigned at randomization – All Randomized and Treated Patients Set (ARTPS)
Table 14.2.1.2 Technical adequacy of perfusion CBV map by off-site readers by treatment arm assigned at randomization and by grade (stratification variable at randomization) – All Randomized and Treated Patients Set (ARTPS)
Table 14.2.1.3 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization – Off-site PPS
Table 14.2.1.4 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site PPS
Table 14.2.1.5 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization – Off-site FAS
Table 14.2.1.6 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site FAS
Table 14.2.1.7 Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site PPS
Table 14.2.1.8 Diagnostic quality of CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site PPS
Table 14.2.1.9 Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site FAS
Table 14.2.1.10 Diagnostic quality of CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site FAS

14.2.2 SECONDARY ANALYSES
Table 14.2.2.1 Intra-reader variability - Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site PPS

Table 14.2.2.2 Intra-reader variability - Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site FAS
Table 14.2.2.3 Inter-reader variability - Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site PPS
Table 14.2.2.4 Inter-reader variability - Diagnostic quality of CBV map by treatment arm assigned at randomization – Off-site FAS
Table 14.2.2.5 Technical adequacy of perfusion CBV map by on-site readers by treatment arm assigned at randomization – All Randomized Patients Set (ARPS)
Table 14.2.2.6 Technical adequacy of perfusion CBV map by on-site readers by treatment arm assigned at randomization and by grade (stratification variable at randomization) – All Randomized Patients Set (ARPS)
Table 14.2.2.7 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization – On-site PPS
Table 14.2.2.8 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – On-site PPS
Table 14.2.2.9 Diagnostic quality of CBV map readers by treatment arm assigned at randomization – On-site PPS
Table 14.2.2.10 Diagnostic quality of CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – On-site PPS
Table 14.2.2.11 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization – On-site FAS
Table 14.2.2.12 Technical adequacy of perfusion CBV map by treatment arm assigned at randomization and by grade (stratification variable at randomization) – On-site FAS
Table 14.2.2.13 Diagnostic quality of CBV map by treatment arm assigned at randomization – On-site FAS
Table 14.2.2.14 Diagnostic quality of CBV map generated assessed by treatment arm assigned at randomization and by grade (stratification variable at randomization) – On-site FAS
Table 14.2.2.15 rCBV by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Comparison between arms – Off-site PPS
Table 14.2.2.16 rCBV by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Comparison within arms – Off-site PPS
Table 14.2.2.17 rCBV by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Comparison between arms – Off-site FAS
Table 14.2.2.18 rCBV by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Comparison within arms – Off-site FAS
Table 14.2.2.19 rCBV by treatment arm assigned at randomization and by grade (according to histopathology) – Comparison between arms – Off-site PPS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.20 rCBV by treatment arm assigned at randomization and by grade (according to histopathology) – Comparison within arms – Off-site PPS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.21 rCBV by treatment arm assigned at randomization and by grade (according to histopathology) – Comparison between arms – Off-site FAS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.22 rCBV by treatment arm assigned at randomization and by grade (according to histopathology) – Comparison within arms – Off-site FAS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.23 Grade assessed by off-site readers (based on rCBV) by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site PPS
Table 14.2.2.24 Grade assessed by off-site readers (based on rCBV) by treatment arm assigned at randomization and by grade (stratification variable at randomization) – Off-site FAS

Table 14.2.2.25 Grade assessed by off-site readers (based on rCBV) by treatment arm assigned at randomization and by grade (according to histopathology) – Off-site PPS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.26 Grade assessed by off-site readers (based on rCBV) by treatment arm assigned at randomization and by grade (according to histopathology) – Off-site FAS - Patients With a Detected Lesion Matching Histopathology
Table 14.2.2.27 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence by treatment arm assigned at randomization at Lesion Level – Off-site PPS
Table 14.2.2.28 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – Off-site PPS
Table 14.2.2.29 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence by treatment arm assigned at randomization at Lesion Level – Off-site FAS
Table 14.2.2.30 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – Off-site FAS
Table 14.2.2.31 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence by treatment arm assigned at randomization at Lesion Level – On-site PPS
Table 14.2.2.32 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence assessed by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – On-site PPS
Table 14.2.2.33 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence assessed by treatment arm assigned at randomization at Lesion Level – On-site FAS
Table 14.2.2.34 Reliability of the T2* signal intensity time curve for diagnosis and level of diagnosis confidence assessed by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – On-site FAS
Table 14.2.2.35 Full-Width at Half-Maximum and Maximum signal drop by treatment arm assigned at randomization at Lesion Level – Off-site PPS
Table 14.2.2.36 Full-Width at Half-Maximum and Maximum signal drop by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – Off-site PPS
Table 14.2.2.37 Full-Width at Half-Maximum and Maximum signal drop by treatment arm assigned at randomization at Lesion Level – Off-site FAS
Table 14.2.2.38 Full-Width at Half-Maximum and Maximum signal drop by treatment arm assigned at randomization and by grade (stratification variable at randomization) at Lesion Level – Off-site FAS

14.3 SAFETY DATA

14.3.1 EXTENT OF EXPOSURE
Table 14.3.1.1 Summary of Study Participation Duration – Safety Set (SS)
Table 14.3.1.2 Administration Modalities of IMPs – Safety Set (SS)
14.3.2 ADVERSE EVENTS
Table 14.3.2.1 Non-Treatment Emergent Adverse Events (NTEAEs) Occuring Before IMP Administration – Overview – Screened Patients Set (SPS)
Table 14.3.2.2 All NTEAEs by Primary System Organ Class and Preferred Term Occuring Before IMP Administration – Safety Set (SS)
Table 14.3.2.3 Treatment Emergent Adverse Events (TEAEs) occuring during the study period whatever the causal relationship – Overview – Safety Set (SS)
Table 14.3.2.4 All TEAEs by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relationship – Safety Set (SS)
Table 14.3.2.5. All TEAEs by Primary System Organ Class and Preferred Term occuring during the study period per causal relationship to IMPs and Study Procedure– Safety Set (SS)
Table 14.3.2.6 TEAEs requiring an AE-targeted medication by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relationship – Safety Set (SS)

Table 14.3.2.7 TEAEs requiring an AE-targeted therapeutic measure by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relatioship – Safety Set (SS)
Table 14.3.2.8 TEAEs requiring an AE-targeted procedure by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relatioship – Safety Set (SS)
Table 14.3.2.9 TEAE requiring trial discontinuation by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relatioship – Safety Set (SS)
Table 14.3.2.10 TEAE requiring IMP interruption by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relatioship – Safety Set (SS)
Table 14.3.2.11 Serious TEAE by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relationship – Safety Set (SS)
Table 14.3.2.12. All Serious TEAEs by Primary System Organ Class and Preferred Term occuring during the study period per causal relationship to IMPs and Study procedure– Safety Set (SS)
Table 14.3.2.13 Serious TEAE leading to death by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relationship – Safety Set (SS)
Table 14.3.2.14 All AESI by Primary System Organ Class and Preferred Term occuring during the study period whatever the causal relationship – Safety Set (SS)
14.3.3 DEATHS, SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS
Table 14.3.3.1 Listing of Deaths - Safety Set (SS)
Table 14.3.3.2 Listing of Serious Adverse Events (other than Deaths) and AESI - Safety Set (SS)
14.3.4 CLINICAL LABORATORY DATA
14.3.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY
14.3.6 CONCOMITANT MEDICATIONS AND PROCEDURES
Table 14.3.6.1 Concomitant Medications According to ATC Classification System –Safety Set (SS)
Table 14.3.6.2 Concomitant Procedures By Primary System Organ Class and Preferred Term – Safety Set (SS)

6.2. Contents of clinical study report section 16.2

16.2 PATIENT DATA LISTING

16.2.1 DISCONTINUED PATIENTS

Listing 16.2.1.1 Patient Disposition – Screened Patient Set (SPS)
Listing 16.2.1.2 Visit Dates – Screened Patient Set (SPS)
Listing 16.2.1.3 End Of Study – Screened Patient Set (SPS)
Listing 16.2.1.4 Inclusion Criteria Not Met at Screening (V1) and MRI / Randomisation Visit (V2) – Screened Patient Set (SPS)
Listing 16.2.1.5 Non-Inclusion Criteria Met at Screening (V1) and MRI / Randomisation Visit (V2) – Screened Patient Set (SPS)

16.2.2 PROTOCOL DEVIATIONS

Listing 16.2.2.1 Protocol Deviations – Screened Patient Set (SPS)

16.2.3 PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Listing 16.2.3.1 Analysis Data Sets – Screened Patient Set (SPS)

16.2.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Listing 16.2.4.1 Demographics At V1 and Weight At V2 – Screened Patient Set (SPS)
Listing 16.2.4.2 Patient Imaging History – Screened Patient Set (SPS)

Listing 16.2.4.3 Study Disease Diagnostic: Glioma – Screened Patient Set (SPS)
Listing 16.2.4.4 Medical History – Screened Patient Set (SPS)
Listing 16.2.4.5 Previous And Concomitant Medications – Screened Patient Set (SPS)
Listing 16.2.4.6 Previous And Concomitant Procedures, Therapeutic Measures – Screened Patient Set (SPS)
Listing 16.2.4.7 MRI examination – Screened Patient Set (SPS)
Listing 16.2.4.8 Pregnancy Test – Screened Patient Set (SPS)

16.2.5 COMPLIANCE AND/OR DRUG CONCENTRATION DATA..... (IF AVAILABLE)

Listing 16.2.5.1 Compliance Of IMPs – Screened Patient Set (SPS)

16.2.6 INDIVIDUAL EFFICACY RESPONSE DATA

Listing 16.2.6.1 Technical adequacy of perfusion CBV map by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.2 Diagnostic quality of CBV map generated by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.3 Technical adequacy of perfusion CBV map and diagnostic quality of CBV map generated by on-site readers – Screened Patient Set (SPS)
Listing 16.2.6.4 rCBV values by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.5 Reliability of the T2* signal intensity time curve in providing sufficient information for diagnosis purpose by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.6 Level of diagnosis confidence by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.7 Reliability of the T2* signal intensity time curve in providing sufficient information for diagnosis purpose and Level of diagnosis confidence by on-site readers – Screened Patient Set (SPS)
Listing 16.2.6.8 Full-Width at Half Maximum by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.9 Maximal Drop by off-site readers – Screened Patient Set (SPS)
Listing 16.2.6.10 Histopathology – Screened Patient Set (SPS)

16.2.7 ADVERSE EVENT LISTINGS (EACH PATIENT)

Listing 16.2.7.1 IMPs administration – Screened Patient Set (SPS)
Listing 16.2.7.2 Non Treatment-Emergent Adverse Events (NTEAEs) – Screened Patient Set (SPS)
Listing 16.2.7.3 Treatment-Emergent Adverse Events (TEAEs) – Screened Patient Set (SPS)
Listing 16.2.7.4 TEAEs per Relationship to IMP: Elucirem® – Screened Patient Set (SPS)
Listing 16.2.7.5 TEAEs per Relationship to IMP: Dotarem® – Screened Patient Set (SPS)
Listing 16.2.7.6 TEAEs per Relationship to Study Procedure – Screened Patient Set (SPS)

16.2.8 . LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY PATIENT, WHEN REQUIRED BY REGULATORY AUTHORITIES

Listing 16.2.8.1 eGFR at Screening (V1) – Screened Patient Set (SPS)

16.2.9 OTHER SAFETY INFORMATION

7. REFERENCES

1. Crisi G, Filice S, Erb G, Bozzetti F. Effectiveness of a High Relaxivity Contrast Agent Administered at Half Dose in Dynamic Susceptibility Contrast MRI of Brain Gliomas. J. Magn Reson Imaging 2017;45: 500–506